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(54) Glycopeptide antibiotic derivatives.

(57) The present invention provides glycopeptide antibiotic derivative compounds. These derivative compounds possess antibacterial activity aginst a wide variety of bacteria, including activity against vancomycin-resistant isolates. Methods of making and using these glycopeptide antibiotic derivative compounds are also provided.

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New improved antibiotics are continually in demand, particularly for the treatment of human diseases. Increased potency, expanded spectrum of bacterial inhibition, increased in vivo efficacy, and improved pharmaceutical properties are some of the goals for improved antibiotics.

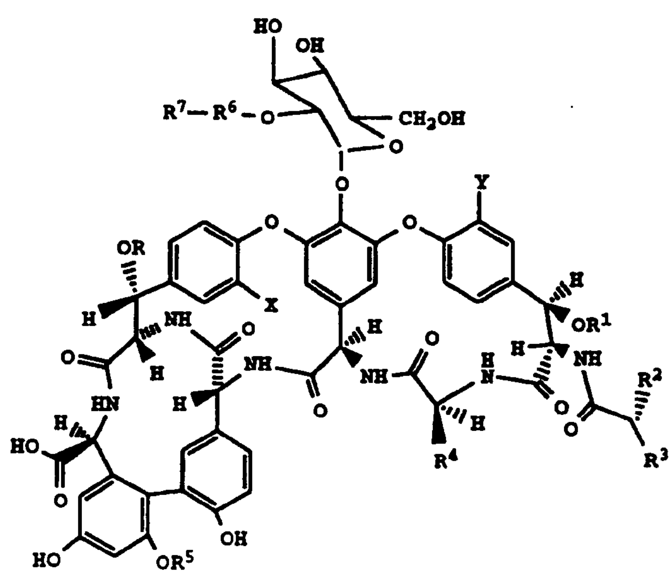
In the search for new antibiotics, structural modification of known antibiotics is attempted whenever possible. The glycopeptide antibiotics have such complex structures that even small changes are difficult. Furthermore, it is difficult to predict the effect these changes will make in the antimicrobial and physiological properties. Processes for modifying known antibiotics and the new active derivatives made by such processes, therefore, continue to be of great importance.

Previously, N-alkyl and N-acyl derivatives of the glycopeptides vancomycin, A51568A, A51568B, M43A and M43D have been prepared (U.S. Patent Nos. 4,639,433, 4,643,987, and 4,698,327). Several of these compounds exhibited microbiological activity, including activity against vancomycin-resistant isolates. Nicas et al., Antimicrobial Agents and Chemotherapy, 33(9):1477-1481 (1989). In addition, European Patent Application Publication No. 0435503, published July 3, 1993, describes certain N-alkyl and N-acyl derivatives of the A82846 glycopeptides, factors A, B, and C.

The formula I compounds of this invention are new members of the glycopeptide group of antibiotics. These new compounds are derivatives of known glycopeptide antibiotics that include vancomycin (U.S. Patent 3,067,099); A82846A, A82846B, and A82846C (U.S. Patent 5,312,738, European Patent Publication 256,071 Al); PA-42867 factors A, C, and D (U.S. Patent 4,946,941 and European Patent Publication 231,111 A2); A83850 (U.S. Patent No. 5,187,082); avoparcin (U.S. Patent 3,338,786 and U.S. Patent 4,322,343); actinoidin, also known as K288 (J. Antibiotics Series A 14:141 (1961); helevecardin (Chem. Abstracts 110:17188 (1989) and Japanese Patent Application 86/157,397); galacardin (Chem. Abstracts 110:17188 (1989) and Japanese Patent Application 89/221,320); and M47767 (European Patent Publication 339,982). The references listed above which describe these glycopeptides are incorporated herein by reference.

Enterococci are important human pathogens. Infections caused by enterococci are generally difficult to treat. Glycopeptides, such as vancomycin and teicoplanin, have become important therapies in the treatment of infections due to enterococci. However, strains of Enterococcus faecium and E. faecalis have recently been isolated that are resistant to vancomycin and teicoplanin. Leclercq et al., "Plasmid Mediated Resistance to Vancomycin and Teicoplanin in Enterococcus Faecium," The New England Journal of Medicine, 319(3):157-161 (1988), and Uttley et al., "Vancomycin-Resistant Enterococci," Lancet, 1:57-58 (1988). The isolates were also found to be resistant to other antibiotics. A recent survey found 7.9% of Enterococci in United States hospitals are now vancomycin resistant. "Nosocomial Enterococci Resistant to Vancomycin" Morbidity and Mortality Weekly Report 42 (30):597-598 (1993). In addition to their broad activity against gram-positive organisms, many of the glycopeptide compounds of this invention also exhibit improved antimicrobial activity against vancomycin-resistant isolates.

The present invention provides compounds of the formula I:



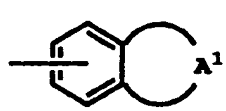
or salt thereof, wherein:

X and Y are each independently hydrogen or chloro;
R is hydrogen, 4-*epi*-vancosaminyl, actinosaminyl, or ristosaminyl;
R^1 is hydrogen, or mannose;
R^2 is $-NH_2$, $-NHCH_3$, or-$N(CH_3)_2$;
R^3 is $-CH_2CH(CH_3)_2$, [*p*-OH, *m*-Cl]phenyl, *p*-rhamnose-phenyl, or [*p*-rhamnose-galactose]phenyl, [*p*-galactose-galactose]phenyl, [*p*-CH_3O-rhamnose]phenyl;
R^4 is $-CH_2(CO)NH_2$, benzyl, [*p*-OH]phenyl, or [*p*-OH, m-Cl]phenyl;
R^5 is hydrogen, or mannose;
R^6 is 4-*epi*-vancosaminyl, L-acosaminyl, L-ristosaminyl, or L-actinosaminyl;
R^7 is $(C_2$-$C_{16})$alkenyl, $(C_2$-$C_{12})$alkynyl, $(C_1$-C_{12} alkyl)-R_8, $(C_1$-C_{12} alkyl)-halo, $(C_2$-C_6 alkenyl)-R_8, $(C_2$-C_6 alkynyl)-R_8, $(C_1$-C_{12} alkyl)-O-R_8, and is attached to the amino group of R^6;
R^8 is selected from the group consisting of:

a) multicyclic aryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:
(i) hydroxy,
(ii) halo,
(iii) nitro,
(iv) $(C_1$-$C_6)$alkyl,
(v) $(C_1$-$C_6)$alkenyl,
(vi) $(C_1$-$C_6)$alkynyl,
(vii) $(C_1$-$C_6)$alkoxy,
(viii) halo-$(C_1$-$C_6)$alkyl,
(ix) halo-$(C_1$-$C_6)$alkoxy,
(x) carbo-$(C_1$-$C_6)$alkoxy,
(xi) carbobenzyloxy,
(xii) carbobenzyloxy substituted with $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo, or nitro,
(xiii) a group of the formula $-S(O)_{n'}$-R^9, wherein n' is 0-2 and R^9 is $(C_1$-$C_6)$alkyl, phenyl, or phenyl substituted with $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo, or nitro, and
(xiv) a group of the formula $-C(O)N(R^{10})_2$ wherein each R^{10} substituent is independently hydrogen, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy, phenyl, or phenyl substituted with $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$-alkoxy, halo, or nitro;

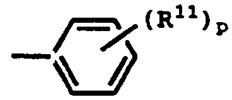
b) heteroaryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:
(i) halo,
(ii) $(C_1$-$C_6)$alkyl,
(iii) $(C_1$-$C_6)$alkoxy,
(iv) halo-$(C_1$-$C_6)$alkyl,
(v) halo-$(C_1$-$C_6)$alkoxy,
(vi) phenyl,
(vii) thiophenyl,
(viii) phenyl substituted with halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkenyl, $(C_1$-$C_6)$alkynyl, $(C_1$-$C_6)$alkoxy, or nitro,
(ix) carbo-$(C_1$-$C_6)$alkoxy,
(x) carbobenzyloxy,
(xi) carbobenzyloxy substituted with $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$ alkoxy, halo, or nitro,
(xii) a group of the formula $-S(O)_{n'}$-R^9, as defined above,
(xiii) a group of the formula $-C(O)N(R^{10})_2$ as defined above, and
(xiv) thienyl;

c) a group of the formula:



wherein A^1 is $-OC(A^2)_2$-$C(A^2)_2$-O-, -O-$C(A^2)_2$-O-,-$C(A^2)_2$-O-, or $-C(A^2)_2$-$C(A^2)_2$-$C(A^2)_2$-$C(A^2)_2$-, and each A^2 substituent is independently selected from hydrogen, $(C_1$-$C_6)$-alkyl, $(C_1$-$C_6)$alkoxy, and $(C_4$-$C_{10})$cycloalkyl;

d) a group of the formula:



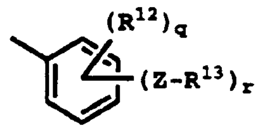
wherein p is from 1 to 5; and

R^{11} is independently selected from the group consisting of:

(i) hydrogen,
(ii) nitro,
(iii) hydroxy,
(iv) halo,
(v) $(C_1\text{-}C_8)$alkyl,
(vi) $(C_1\text{-}C_8)$alkoxy,
(vii) $(C_9\text{-}C_{12})$alkyl,
(viii) $(C_2\text{-}C_9)$alkynyl,
(ix) $(C_9\text{-}C_{12})$alkoxy,
(x) $(C_1\text{-}C_3)$alkoxy substituted with $(C_1\text{-}C_3)$alkoxy, hydroxy, halo$(C_1\text{-}C_3)$alkoxy, or $(C_1\text{-}C_4)$alkylthio,
(xi) $(C_2\text{-}C_5)$alkenyloxy,
(xii) $(C_1\text{-}C_{13})$alkynyloxy
(xiii) halo-$(C_1\text{-}C_6)$alkyl,
(xiv) halo-$(C_1\text{-}C_6)$alkoxy,
(xv) $(C_2\text{-}C_6)$alkylthio,
(xvi) $(C_2\text{-}C_{10})$alkanoyloxy,
(xvii) carboxy-$(C_2\text{-}C_4)$alkenyl,
(xviii) $(C_1\text{-}C_3)$alkylsulfonyloxy,
(xix) carboxy-$(C_1\text{-}C_3)$alkyl,
(xx) N-[di$(C_1\text{-}C_3)$-alkyl]amino-$(C_1\text{-}C_3)$alkoxy,
(xxi) cyano-$(C_1\text{-}C_6)$alkoxy, and
(xxii) diphenyl-$(C_1\text{-}C_6)$alkyl,

with the proviso that when R^{11} is $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$alkoxy, or halo, p must be greater or equal to 2, or when R^7 is $(C_1\text{-}C_3$ alkyl$)\text{-}R^8$ then R^{11} is not hydrogen, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_8)$alkoxy, or halo;

e) a group of the formula:



wherein q is 0 to 4;

R^{12} is independently selected from the group consisting of:

(i) halo,
(ii) nitro,
(iii) $(C_1\text{-}C_6)$alkyl,
(iv) $(C_1\text{-}C_6)$alkoxy,
(v) halo-$(C_1\text{-}C_6)$alkyl,
(vi) halo-$(C_1\text{-}C_6)$alkoxy, and
(vii) hydroxy, and
(vii) $(C_1\text{-}C_6)$thioalkyl;

r is 1 to 5; provided that the sum of q and r is no greater than 5;

Z is selected from the group consisting of:

(i) a single bond,
(ii) divalent $(C_1\text{-}C_6)$alkyl unsubstituted or substituted with hydroxy, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy,
(iii) divalent $(C_2\text{-}C_6)$alkenyl,
(iv) divalent $(C_2\text{-}C_6)$alkynyl, or
(v) a group of the formula $\text{-}(C(R^{14})_2)_s\text{-}R^{15}\text{-}$ or $\text{-}R^{15}\text{-}(C(R^{14})_2)_s\text{-}$, wherein s is 0-6; wherein each R^{14} substituent is independently selected from hydrogen, $(C_1\text{-}C_6)$-alkyl, or $(C_4\text{-}C_{10})$ cycloalkyl; and R^{15} is selected from -O-, -S-, -SO-, $\text{-}SO_2\text{-}$, $\text{-}SO_2\text{-}O\text{-}$, -C(O)-, -OC(O)-, -C(O)O-, -NH-, $\text{-}N(C_1\text{-}C_6$ alkyl$)\text{-}$, and

-C(O)NH-, -NHC(O)-, N=N;

R^{13} is independently selected from the group consisting of:

(i) (C_4-C_{10})heterocyclyl,

(ii) heteroaryl,

(iii) (C_4-C_{10})cycloalkyl unsubstituted or substituted with (C_1-C_6)alkyl, or

(iv) phenyl unsubstituted or substituted with 1 to 5 substituents independently selected from: halo, hydroxy, nitro, (C_1-C_{10}) alkyl, (C_1-C_{10})alkoxy, halo-(C_1-C_3)alkoxy, halo-(C_1-C_3)alkyl, (C_1-C_3)alkoxyphenyl, phenyl, phenyl-(C_1-C_3)alkyl, (C_1-C_6)alkoxyphenyl, phenyl-(C_1-C_3)alkynyl, and (C_1-C_6)alkylphenyl;

f) (C_4-C_{10})cycloalkyl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

(i) (C_1-C_6)alkyl,

(ii) (C_1-C_6)alkoxy,

(iii) (C_1-C_6)alkenyl,

(iv) (C_1-C_6)alkynyl,

(v) (C_4-C_{10})cycloalkyl,

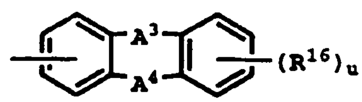
(vi) phenyl,

(vii) phenylthio,

(viii) phenyl substituted by nitro, halo, (C_1-C_6)alkanoyloxy, or carbocycloalkoxy, and

(ix) a group represented by the formula -Z-R^{13} wherein Z and R^{13} are as defined above; and

g) a group of the formula:



wherein

A^3 and A^4 are each independently selected from

(i) a bond,

(ii) -O-,

(iii) -S(O)$_t$-, wherein t is 0 to 2,

(iv) -C(R^{17})$_2$-, wherein each R^{17} substituent is independently selected from hydrogen, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or both R^{17} substituents taken together are O,

(v) -N(R^{18})$_2$-, wherein each R^{18} substituent is independently selected from hydrogen; (C_1-C_6)alkyl; (C_1-C_6)alkenyl; (C_1-C_6)alkynyl; (C_4-C_{10})cycloalkyl; phenyl; phenyl substituted by nitro, halo, (C_1-C_6)alkanoyloxy; or both R^{18} substituents taken together are (C_4-C_{10})cycloalkyl;

R^{16} is R^{12} or R^{13} as defined above; and

u is 0-4.

Another aspect of the invention relates to compositions for the treatment of susceptible bacterial infections comprising a compound of formula I in combination with an acceptable pharmaceutical carrier. Methods for the treatment of susceptible bacterial infections with compositions of formula I are also a part of this invention.

The alkyl substituents recited herein denote substituted or unsubstituted, straight or branched chain hydrocarbons of the length specified. The term "alkenyl" refers to a substituted or unsubstituted, straight or branched alkenyl chain of the length specified. The term "alkynyl" refers to a substituted or unsubstituted, straight or branched alkynyl chain of the length specified.

The alkoxy substituents recited herein represent an alkyl group attached through an oxygen bridge. The term "alkenoxy" represents a alkenyl chain of the specified length attached to an oxygen atom.

The term "multicyclic aryl" means a stable, saturated or unsaturated, substituted or unsubstituted, 9 to 10 membered organic fused bicyclic ring; a stable, saturated or unsaturated, substituted or unsubstituted 12 to 14 membered organic fused tricyclic ring; or a stable, saturated or unsaturated, substituted or unsubstituted 14 to 16 membered organic fused tetracyclic ring. The bicyclic ring may have 0 to 4 substituents, the tricyclic ring may have 0 to 6 substituents, and the tetracyclic ring may have 0 to 8 substituents. Typical multi-cyclic aryls include fluorenyl, napthyl, anthranyl, phenanthranyl, biphenylene and pyrenyl.

The term "heteroaryl" represents a stable, saturated or unsaturated, substituted or unsubstituted, 4 to 7 membered organic monocyclic ring having a hetero atom selected from S, O, and N; a stable, saturated or unsaturated, substituted or unsubstituted, 9 to 10 membered organic fused bicyclic ring having 1 to 2 hetero atoms selected from S, O, and N; or a stable, saturated or unsaturated, substituted or unsubstituted, 12 to 14 membered organic fused tricyclic ring having a hetero atom selected from S, O, and N. The nitrogen and sulfur

atoms of these rings are optionally oxidized, and the nitrogen hetero atoms are optionally quarternized. The monocyclic ring may have 0 to 5 substituents. The bicyclic ring may have 0 to 7 substituents, and the tricyclic ring may have 0 to 9 substituents. Typical heteroaryls include quinolyl, piperidyl, thienyl, piperonyl, oxafluorenyl, pyridyl and benzothienyl and the like.

The term "(C_4-C_{10})cycloalkyl" embraces substituents having from four to ten carbon atoms, such as cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl which may be unsubstituted or substituted with substituents such as alkyl and phenyl. This term also embraces C_5 to C_{10} cycloalkenyl groups such as cyclopentenyl and cyclohexenyl. The term "(C_4-C_{10})cycloalkyl" also embraces bicyclic and tricyclic cycloalkyls such as bicyclopentyl, bicylohexyl, bicycloheptyl, and adamantyl.

The term "alkanoyloxy" represents an alkanoyl group attached through an oxygen bridge. These substituents may be substituted or unsubstituted, straight, or branched chains of the specified length.

The term "cyano-(C_1-C_6)alkoxy" represents a substituted or unsubstituted, straight or branched alkoxy chain having from one to six carbon atoms with a cyano moiety attached to it.

The term "divalent (C_1-C_6)alkyl" represents an unsubstituted or substituted, straight or branched divalent alkyl chain having from one to six carbon atoms. Typical divalent (C_1-C_6)alkyl groups include methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, t-butylene, pentylene, neo-pentylene, and hexylene. Such divalent (C_1-C_6)alkyl groups may be substituted with substituents such as alkyl, alkoxy, and hydroxy.

The term "divalent (C_2-C_6)alkenyl" represents a straight or branched divalent alkenyl chain having from two to six carbon atoms. Typical divalent (C_2-C_6)alkenyl include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl and the like.

The term "divalent (C_2-C_6)alkynyl" represents a straight or branched divalent alkynyl chain having from two to six carbon atoms. Typical divalent (C_2-C_6)alkynyl include ethynylene, 1-propynylene, 2-propynylene, 1-butynylene, 2-butynylene and the like.

The term "halo" represents chloro, fluoro, bromo or iodo.

The term "halo-(C_1-C_6)alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms with from 0 to 3 halogen atoms attached to each carbon. Typical halo-(C_1-C_6)alkyl groups include chloromethyl, 2-bromoethyl, 1-chloroisopropyl, 3-fluoropropyl, 2,3-dibromobutyl, 3-chloroisobutyl, iodo-t-butyl, trifluoromethyl, and the like.

The term "halo-(C_1-C_6)alkoxy" represents a straight or branched alkoxy chain having from one to six carbon atoms with from 0 to 3 halogen atoms attached to each carbon. Typical halo-(C_1-C_6)alkoxy groups include chloromethoxy, 2-bromoethoxy, 1-chloroisopropoxy, 3-fluoropropoxy, 2,3-dibromobutoxy, 3-chloroisobutoxy, iodo-*t*-butoxy, trifluoromethoxy, and the like.

The term "heterocyclyl" embraces saturated groups having three to ten ring members and which heterocyclic ring contains a hetero atom selected from oxygen, sulfur and nitrogen, examples of which are piperazinyl, morpholino, piperdyl, methylpiperdyl, azetidinyl, and aziridinyl.

The invention includes salts of the compounds defined by formula I. Although generally neutral, a compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula I which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an inorganic base. Such salts are known as acid addition and base addition salts.

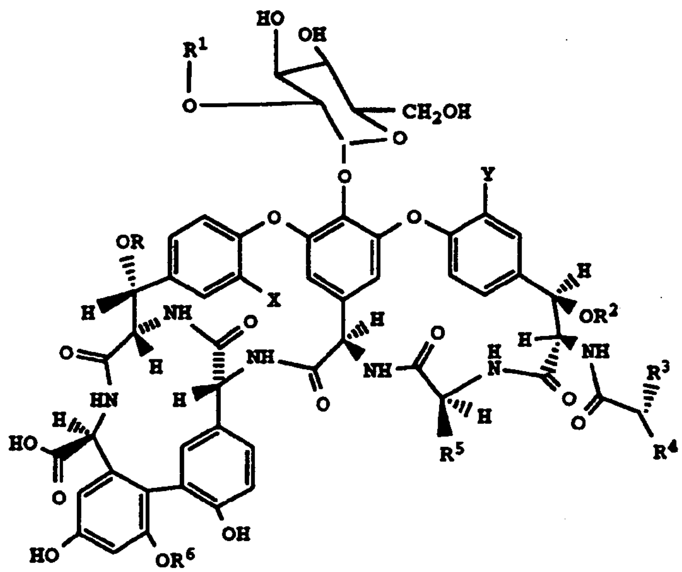
Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic acid, methanesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, g-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid, acetic acid, and methanesulfonic

acid.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

The compounds of the present invention are prepared from compounds of the formula:



Formula II

The compounds of formula II are defined in Table 1.

TABLE 1

Formula II Compounds[a]

antibiotic	R	R^1	R^2	R^3	R^4	R^5	R^6	X	Y
vancomycin	H	van	H	$NHCH_3$	$CH_2CH(CH_3)_2$	$CH_2(CO)NH_2$	H	Cl	Cl
A82846A	4-epi	4-epi	H	$NHCH_3$	$CH_2CH(CH_3)_2$	$CH_2(CO)NH_2$	H	H	Cl
A82846B	4-epi	4-epi	H	$NHCH_3$	$CH_2CH(CH_3)_2$	$CH_2(CO)NH_2$	H	Cl	Cl
A82846C	4-epi	4-epi	H	$NHCH_3$	$CH_2CH(CH_3)_2$	$CH_2(CO)NH_2$	H	H	H
PA-42867-A	4-epi	4-epi	H	$NHCH_3$	$CH_2CH(CH_3)_2$	$CH_2(CO)NH_2$	H	Cl	H
PA-42867-C	4-epi	4-epi	H	$NHCH_3$	$CH_2CH(CH_3)_2$	$CH_2(CO)NH_2$	H	H	H
PA-42867-D	4-epi	4-epi	H	$N(CH_3)_2$	$CH_2CH(CH_3)_2$	$CH_2(CO)NH_2$	H	Cl	H
A83850A	H	keto	H	$N(CH_3)_2$	$CH_2CH(CH_3)_2$	$CH_2(CO)NH_2$	H	Cl	Cl
A83850B	H	keto	H	$NHCH_3$	$CH_2CH(CH_3)_2$	$CH_2(CO)NH_2$	H	Cl	Cl
actinoidin	actin	acos	H	NH_2	p-OH,m-Cl-phenyl	benzyl	man	Cl	H
avoparcin	risto	risto	man	$N(CH_3)_2$	p-rha-phenyl	p-OH-phenyl	H	H	H
galacardin	risto	risto	man	$NHCH_3$	p-gal-gal-phenyl	p-OH-phenyl	H	Cl	H
helevecardin	risto	risto	H or man	$NHCH_3$	p-CH_3O-rha-phenyl	p-OH,m-Cl-phenyl	H	Cl	H
M47767	actin	acos	H	$NHCH_3$	p-OH,m-Cl-phenyl	benzyl	man	Cl	H

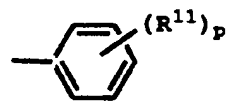
[a]Abbreviations for the formula II compounds are: actin = actinosaminyl; acos = acosaminyl; 4-epi = 4-epi-vancosaminyl; gal = galactosyl; keto = 4-keto-vancosaminyl; man = mannose; rha = rhamnosyl; rha-gal = rhamnosyl-galactosyl; risto = ristosaminyl; van = vancosaminyl.

In a preferred embodiment of the invention, the formula I compounds are prepared from the A82846 antibiotics (A82846A, A82846B, and A82846C) and PA-42867-A. In a more preferred embodiment, the compounds of the present invention are prepared from A82846B ("A82846B derivatives"). A82846B is represented by formula I compounds wherein R is 4-*epi*-vancosaminyl, R^1 is hydrogen, R^2 is $NHCH_3$, R^3 is $CH_2CH(CH_3)_2$, R^4 is $CH_2(CO)NH_2$, R^5 is hydrogen, R^6 is 4-*epi*-vancosaminyl and X and Y are Cl. A82846B derivatives of the present invention having substituents at position R^7 of formula I are list herein in the manner "R^7-A82846B". For example, the compound "phenylbenzyl-A82846B" has a phenylbenzyl substituent at position R^7 in formula I.

Preferred formula I compounds include those A82846B derivatives wherein R^7 is -(C_1-C_{12}-alkyl)-R^8, with -CH_3-R^8 being more preferred, and R^8 is an unsubstituted multicyclic aryl. Of this group, naphthylmethyl-A82846B, acenapthlenyl-methyl-A82846B, and fluorenylmethyl-A82846B are more preferred.

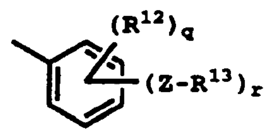
Preferred formula I compounds also include those A82846B derivatives wherein R^7 is -(C_1-C_{12}-alkyl)-R^8, with -CH_3-R^8 being more preferred, and R^8 is an unsubstituted heteroaryl or a heteroaryl substituted by halophenyl. Of this group, [1-oxa]fluorenylmethyl-A82846B, chlorophenylbenzoxazolemethyl-A82846B, and phenylthienylmethyl-A82846B are more preferred.

Further preferred compounds of formula I include those A82846B derivatives wherein R^7 is -(C_1-C_{12}-alkyl)-R^8, with -CH_3- R^8 being more preferred, and R^8 is a group of the formula:



wherein p is 1 and R^{11} is selected from (C_2-C_5)alkenyloxy, halo-(C_1-C_6)alkoxy, (C_2-C_{10})alkanoyloxy, (C_1-C_3)alkoxy substituted with (C_1-C_4)alkylthio, and diphenyl-(C_1-C_6)alkyl. Of this group, trifluromethoxybenzyl-A82846B, diphenylmethylbenzyl-A82846B, thiopropylethoxybenzyl-A82846B, acetoxybenzyl-A82846B, nonanoyloxybenzyl-A82846B, and tetrafluoroethoxybenzyl-A82846B are more preferred.

Still further preferred compounds of formula I include those A82846B derivatives wherein R^7 is -(C_1-C_{12}-alkyl)-R^8, with -CH_3-R^8 being more preferred, and R^8 is a group of the formula:



wherein q is 1 to 5; r is 1; Z is selected from a single bond, divalent (C_1-C_6)alkyl, divalent (C_2-C_6)alkenyl, and -R^{15}-$(C(R^{14})_2)_s$-, wherein R^{15} is selected from -O-, -S-, -SO_2-, and -OC(O)-, each R^{14} substituent is hydrogen, and s is 0 or 1; and R^{13} is selected from: (C_4-C_{10})cycloalkyl; phenyl; and phenyl substituted by nitro, halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, or halo(C_1-C_3)alkyl. Of this group, chlorophenylbenzyl-A82846B, phenylbenzyl-A82846B, benzylbenzyl-A82846B, methylphenylbenzyl-A82846B, pentylphenylbenzyl-A82846B, methoxyphenylbenzyl-A82846B, pentoxyphenylbenzyl-A82846B, nitrophenoxybenzyl-A82846B, fluorophenylbenzyl-A82846B, phenylethynylbenzyl-A82846B, phenoxybenzyl-A82846B, benzyloxybenzyl-A82846B, nitrophenylbenzyl-A82846B, chlorophenoxybenzyl-A82846B, chlorobenzyloxybenzyl-A82846B, butylphenoxybenzyl-A82846B, trifluoromethylphenoxybenzyl-A82846B, dichlorophenoxybenzyl-A82846B, nitrobenzyloxybenzyl-A82846B, benzoyloxybenzyl-A82846B, cyclohexyloxybenzyl-A82846B, cyclohexanoyloxybenzyl-A82846B, thiophenylbenzyl-A82846B, chlorophenylsulfonylbenzyl-A82846B, and cyclohexylbenzyl-A82846B, cyclohexylethoxybenzyl-A82846B chlorophenoxynitro-benzyl-A82846B benzylmethoxybenzyl-A82846B, chlorophenoxynitro-benzyl-A82846B, and phenoxymethoxybenzyl-A82846B, benzoyloxy-dimethoxybenzyl-A82846B, cyclohexanoyloxydimethylbenzyl-A82846B, trifluoromethylphenylbenzyl-A82846B, butylphenylthiobenzyl-A82846B, and bromophenylbenzyl-A82846B more preferred.

Still further preferred compounds of formula I include A82846B derivatives wherein R^7 is -(C_1-C_{12}-alkyl)-R^8, with -CH_3- R^8 being more preferred, and R^8 is (C_4-C_{10})cycloalkyl substituted with (C_4-C_{10})cycloalkyl. Of this group of compounds, more preferred is cyclohexyl-cyclohexylmethyl-A82846B and butylcyclohexylmethyl-A82846B.

Formula I compounds that are prepared from A83850A or A83850B can be prepared from the reduced forms of these compounds. The reduced forms of compounds A83850A or A83850B are produced according to the method described in U.S. Pat. No. 5,187,082, which is incorporated herein by reference.

The compounds of this invention are prepared by reacting a formula II compound with an aldehyde to form an intermediate Schiff's base, which is subsequently reduced with a metal borohydride to give the desired N-alkyl amine.

In the first method of making the compounds of this invention, hereinafter Method A (described in Examples 1 and 2), the reaction for the formation of the Schiff's base is carried out under an inert atmosphere, such as nitrogen or argon, in a polar solvent, such as dimethylformamide (DMF) or methanol (MeOH), or a mixture of polar solvents, such as a mixture of dimethylformamide and methanol, at a temperature of about 25°C to about 100°C. The reaction is preferably carried out at a temperature from about 60°C to about 70°C for 30 minutes to 2 hours in a mixture of dimethylformamide and methanol, or in methanol. The intermediate Schiff's base is then reduced, preferably without isolation, to produce the corresponding N-alkyl derivative(s). The reduction of the Schiff's base can be effected using a chemical reducing agent such as a metal borohydride, for example, sodium borohydride or sodium cyanoborohydride. The reduction reaction can be carried out in a polar organic solvent, such as dimethylformamide, methanol, or a mixture of polar solvents, such as a mixture of dimethylformamide and methanol. The reduction reaction can be carried out at a temperature of about 25°C to about 100°C for 1 to 5 hours. The reduction reaction is preferably carried out using an excess of sodium cyanobor-

ohydride in a mixture of dimethylformamide and methanol or in methanol at about 60°C to about 70°C for 1 to 2 hours. Method A is preferable for benzylic aldehydes.

In a second method of making compounds of this invention, hereinafter Method B (described in Example 3), the formation of the Schiff's base is carried out under an inert atmosphere, such as nitrogen or argon, in the presence of the reducing agent, sodium cyanoborohydride, in a polar solvent, such as dimethylformamide, methanol, or a mixture of polar solvents, such as a mixture of dimethylformamide and methanol, at a temperature of about 25°C to about 100°C for 1 to 5 hours. The reaction is preferably carried out at a temperature from about 60°C to about 70°C for 1 to 2 hours in a mixture of dimethylformamide and methanol. Method B is preferable for nonbenzylic aldehydes.

In a third method of making compounds of this invention, hereinafter Method C (described in Example 4), the formation of the Schiff's base is carried out a) under an inert atmosphere, such as nitrogen or argon, b) in the presence of the reducing agent, such as a metal borohydride, with sodium cyanoborohydride being most preferred, or a homogenous or heterogeneous catalytic hydrogenation agent(s), such as Crabtree's catalyst, Wilkinson's catalyst, palladium on carbon, platinum on carbon, or rhodium on carbon, c) in a polar solvent, such as dimethylformamide, methanol, or a mixture of polar solvents, such as a mixture of dimethylformamide and methanol, and d) at a temperature of about 25°C to about 100°C. The reaction is preferably carried out at a temperature from about 60°C to about 70°C in methanol. The reaction is allowed to continue for about 20 to about 28 hours, at which time the reaction mixture is adjusted to about pH 7.5 to about pH 10, with a pH of about 9.0 being preferred. The pH adjustment halts the reaction. Because the product is marginally soluble in polar solvents, the solvent of the reaction can be exchanged to an alcohol such as ethanol, butanol, or isopropanol, with isopropanol being preferred, to allow for precipitation of the product. Method C is a preferred method of this invention in view of the increased product yield provided by this method. Another advantage of this reaction scheme is the increased ratio of preferred product (products substituted at the amino group of the sugar denoted as R^1 in Formula II compounds) to other products (products that are substituted at the amino groups of substitutents denoted as R and/or R^3 of the Formula II compounds). By allowing the reaction to proceed for an extended period of time, such as 20 to 28 hours, products that are monosubstituted at positions denoted as R and R^3 in the Formula II compounds are converted to disubstituted forms, making the preferred monosubstituted derivative easier to isolate.

The products of the reaction, obtained from either Method A, B, or C can be purified by preparative reverse-phase HPLC utilizing Waters C18 Nova-Pak columns with ultraviolet light (UV; 235 nm or 280 nm) detection. A 30 minute gradient solvent system consisting of 95% aqueous buffer/5% CH_3CN at time=0 minutes to 20% aqueous buffer/80% CH_3CN at time=30 minutes is typically used, where the aqueous buffer is either TEAP (0.5% aqueous triethylamine adjusted to pH=3 with phosphoric acid) or TFA (0.1% trifluoroacetic acid overall concentration).

HPLC analysis of the reaction mixtures and final purified products can be accomplished utilizing a Waters C18 MicroBonda-Pak column (typically 3.9 x 300 mm steel) or Waters Nova-pak C18 RCM column (8 x 100 mm) with UV (235 nm or 280 nm) detection. A 30 minute gradient solvent system consisting of 95% aqueous buffer/5% CH_3CN at time=0 minute to 20% aqueous buffer/80% CH_3CN at time=30 minutes is typically used, where the aqueous buffer is either TEAP (0.5% aqueous triethylamine adjusted to pH=3 with phosphoric acid) or TFA (0.1% trifluoroacetic acid overall concentration).

The ratio of the aldehyde to the formula II compound and the reaction conditions determines the products of the reaction. The monosubstituted derivatives are those derivatives where a hydrogen atom of the amino group at position R^1 in formula II is replaced by one of the substituents listed above for formula I. When using Methods A or B, described above, the formation of monosubstituted derivatives substituted at the amino group of the amino sugar at position R^1 in the formula II compounds is favored by using a slight excess of aldehyde, a shorter reaction time, and a lower temperature. As noted above, Method C favors the formation of the monosubstituted derivative. The monosubstituted derivative is preferred. A large excess of the aldehyde favors the formation of disubstituted and trisubstituted derivatives of the formula II compounds. The disubstituted derivatives are the derivatives where a hydrogen atom at two of the locations selected from the amino group at position $R^{3'}$ and the amino group of the amino sugars designated as R or R^1 in formula II, are replaced by the reduced aldehyde moiety. The trisubstituted derivatives are the derivatives where a hydrogen atom at three of the locations selected from the amino group at position $R^{3'}$ and the amino group of the amino sugars designated as R or R^1 in formula II, are replaced by the reduced aldehyde moiety.

Examples of compounds that have been prepared and are illustrative of the formula I compounds are listed in Tables 2A and 2B. Table 2A lists compounds prepared by reacting an aldehyde with the glycopeptide A82846B. Table 2A lists the sidechain substitutions on the amino group of the 4-*epi*-vancosaminyl sugar of the 4-*epi*-vancosaminyl-O-glycosyl disaccharide of the A82846B compound. All of the compounds listed are monosubstituted derivatives.

Table 2B lists those compounds that were prepared by reacting an aldehyde with a variety of glycopeptide antibiotics other than A82846B. The compounds of Table 2B are monosubstituted at the amino group of the amino sugar designated as R^1 in formula II with the sidechain listed. All of the compounds listed are monosubstituted derivatives.

TABLE 2A

COMPOUND NO.	SIDECHAIN
1	2-naphthylmethyl
2	4-phenylbenzyl
3	1-naphthylmethyl
4	4-phenoxybenzyl
5	4-benzyloxybenzyl
6	4-trifluoromethoxybenzyl
7	4-allyloxylbenzyl
8	4-nonyloxybenzyl
9	2-methoxy-1-naphthylmethyl
10	4-dodecyloxybenzyl
11	9-phenanthranylmethyl
12	4-decyloxybenzyl
13	9-anthranylmethyl
14	4-[phenylethynyl]4-phenylbenzyl
15	4-methoxy-1-naphthylmethyl
16	1-pyrenylmethyl
17	9-[10-methyl]anthranylmethyl
18	9-[10-chloro]anthranylmethyl
19	2-benzthienylmethyl
20	4-[4-hydroxyphenyl]benzyl
21	4-[4-octylphenyl]benzyl
22	4-[4-pentylphenyl]benzyl
23	4-[4-octyloxyphenyl]benzyl
24	3-pyridylmethyl
25	5-nitro-1-naphthylmethyl
26	4-pyridylmethyl
27	4-quinolylmethyl
28	3-quinolylmethyl
29	4-stilbenzyl
30	2-quinolylmethyl
31	2-pyridylmethyl
32	2-fluorenylmethyl
33	4-phenoxyphenethyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
34	4-[4-pentylcyclohexyl]benzyl
35	4-benzylphenethyl
36	4-[4-biphenyl]benzyl
37	4-trifluoromethylbenzyl
38	trans-cinnamyl
39	4-[1-oxa]fluorenylmethyl
40	4-[4-pentoxyphenyl]benzyl
41	4-thiomethylbenzyl
42	2,3-[2-methyl-3-[4-t-butylphenyl]]propenyl
43	9-(1-methyl)-acridinylmethyl
44	2-hydroxy-1-naphthylmethyl
45	4-[2-phenyl-6-methoxy]quinoylmethyl
46	4-diphenylmethylbenzyl
47	3,4 cyclohexenylmethyl
48	3,4-methylenedioxylbenzyl
49	3-phenoxybenzyl
50	4-benzylbenzyl
51	3-benzyloxy-6-methoxy benzyl
52	4-benzyloxy-3-methoxybenzyl
53	3,4-dibenzyloxybenzyl
54	4-[4-methoxyphenyl]benzyl
55	4-[3-cyanopropoxy]benzyl
56	3,4-ethylenedioxybenzyl
57	4-[4-nitrophenoxy]benzyl
58	2,3-methylenedioxybenzyl
59	2-benzyloxyphenethyl
60	2-ethoxy-1-naphthylmethyl
61	2-benzylfurylmethyl
62	3-phenoxyphenethyl
63	4-phenoxyphenethyl
64	4-[4-nitrophenyl]benzyl
65	6-methoxy-2-naphthylmethyl
66	3-methyl-5-thienylmethyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
67	5-phenyl-2-thienylmethyl
68	4-benzyloxyphenethyl
69	3-benzyloxyphenethyl
70	4-[2-nitrophenoxy]benzyl
71	5-[4-methoxyphenyl]-2-thienylmethyl
72	4-difluormethoxybenzyl
73	2,3,4,5,6-pentamethylbenzyl
74	5-iodo-2-thienylmethyl
75	4-[2-[2-chloroethoxy]ethoxy]benzyl
76	3,4-dimethylbenzyl
77	3-acetoxybenzyl
78	4-nitrobenzyl
79	4-phenylethynylbenzyl
80	4-[2-chloro-6-fluorobenzyloxy]benzyl
81	4-[3,4-dichlorophenoxy]benzyl
82	5-[2,3-dihydrobenzfuryl]methyl
83	4-[2-(N,N-diethylamino)ethoxy]benzyl
84	2-bicyclo[2.1.2]heptylmethyl
85	2-hydroxy-5-phenylbenzyl
86	3-[4-chlorophenoxy]benzyl
87	4-[3-chlorophenoxy]-3-nitrobenzyl
88	4-[2-chlorophenoxy]-3-nitrobenzyl
89	3,5-dimethylbenzyl
90	4-[4-ethylphenyl]benzyl
91	3-phenylbenzyl
92	4-[3-fluorophenyl]benzyl
93	4-[4-chlorobenzyloxy]benzyl
94	4-[4-chlorophenoxy]-3-nitrobenzyl
95	4-[4-methylphenoxy]benzyl
96	4-[4-t-butylphenoxy]benzyl
97	4-[4-methylphenyl]benzyl
98	4-[4-methoxyphenoxy]benzyl
99	4-acetoxy-3-methoxybenzyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
100	4-[(2-phenyl)ethyl]benzyl
101	3-[5-phenyl]pyridinylmethyl
102	4-[2-nitrophenyl]benzyl
103	2-[1-hydroxy]fluorenylmethyl
104	4-benzyl-3-methoxybenzyl
105	4-[cyclohexylmethoxy]-3-ethoxybenzyl
106	3-[3,3'-dichlorophenoxy]benzyl
107	4-[4-propylphenyl]benzyl
108	4-thiophenylbenzyl
109	4-[alpha-hydroxybenzyl]benzyl
110	2,2-dinitro-4-thiophenebenzyl
111	3-[3-trifluoromethylphenoxy]benzyl
112	4-[t-butylethynyl]benzyl
113	4-phenoxy-3-methoxy-benzyl
114	4-[3-trifluoromethylphenoxy]-3-nitrobenzyl
115	2-phenylthiobenzyl
116	2-[4-chlorophenyl]-6-benzoxazolemethyl
117	4-[alpha-methoxybenzyl]benzyl
118	4-cyclohexylbenzyl
119	3-[3,4-dichlorophenoxy]benzyl
120	acenaphthlenylmethyl
121	4-[1,1,2,2-tetrafluoroethoxy]benzyl
122	4-benzoyloxy-3,3'-dimethoxybenzyl
123	3-[cyclohexylmethoxy]benzyl
124	4-cyclohexyloxybenzyl
125	3-[2-quinoylmethoxy]benzyl
126	4-[alpha-ethoxybenzyl]benzyl
127	4-[cyclohexylethoxy]benzyl
128	4-[alpha-propoxybenzyl]benzyl
129	4-[4-methyl-1-piperidino]benzyl
130	2-thiophene-1,2-cyclohexenylmethyl
131	4-[4-nitrobenzyloxy]benzyl
132	3-[4-trifluoromethylphenoxy]benzyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
133	3-benzoyl-2,4-dichlorobenzyl
134	4-[2-(2-thiopropyl)ethoxy]benzyl
135	4-[2-methyl-1-piperidino]benzyl
136	4-hydroxybenzyl
137	4-[2-pyridyl]benzyl
138	4-acetoxybenzyl
139	5,6-benzonorbornylmethyl
140	3-phenylcyclopentylmethyl
141	1-adamantylmethyl
142	3-[cyclohexylmethoxy]-4-methoxybenzyl
143	2-[2-glucosyl]benzyl
144	4-[4-pentoxybiphenyl]benzyl
145	3,4-dihydroxybenzyl
146	4-[4-methylpiperazino]benzyl
147	4-morpholinobenzyl
148	4-[4-chlorophenylsulfonyl]benzyl
149	4-methylsulfonyloxybenzyl
150	4-benzoyloxybenzyl
151	5-phenyl-3-pyridinylmethyl
152	4-[N,N-bis(2-chloroethyl)amino]benzyl
153	3-cyclohexyloxybenzyl
154	4-[2-t-butoxyethoxy]benzyl
155	3,3'-dichloro-4-hydroxy-benzyl
156	1,2,3,4,-tetrahydro-9-anthranylmethyl
157	4-cyclohexanoyloxybenzyl
158	4-nonanoyloxybenzyl
159	4-[phenylsulfinyl]benzyl
160	4-anilinobenzyl
161	cyclohexylmethyl
162	3-benzoyloxybenzyl
163	3-nonanoyloxybenzyl
164	4-[cyclohexyl]cyclohexylmethyl
165	3-cyclohexanoyloxybenzyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
166	4-[cyclohexanoyloxy]-3,3'-[dimethoxy]benzyl
167	4-[nonanoyloxy]-3,3'-[dimethoxy]benzyl
168	1,2,3,4-tetrahydro-6-naphthylmethyl
169	2-hydroxybenzyl
170	[2-[6,6-dimethyl-bicyclo[3.1.1]hept-2-enyl]methyl
171	1-cyclohexenyl-4-isopropylmethyl
172	4-[4-methoxyphenyl]butyl
173	4-[[2,3,4,5,6-pentamethyl]phenylsulfonyloxy]benzyl
174	4-[1-pyrrolidinosulfonyl]benzyl
175	3-[4-methoxyphenyl]propyl
176	8-phenyloctyl
177	4-[2,3-dihydroxypropoxy]benzyl
178	4-[N-methylanilino]benzyl
179	2-[2-napthyl]ethyl
189	6-methyl-2-naphthylmethyl
190	cis-bicyclo[3.3.0]octane-2-methyl
191	2-tridecynyl
192	4-butyl-2-cyclohexylmethyl
193	4-[(4-fluorobenzoyl)amino]benzyl
194	4-[(3-fluorobenzoyl)amino]benzyl
195	8-phenoxyoctyl
196	6-phenylhexyl
197	10-phenyldecyl
198	8-bromooctyl
199	11-tridecynyl
200	8-[4-methoxyphenoxy]octyl
201	8-[4-phenylphenoxy]octyl
202	8-[4-phenoxyphenoxy]octyl
203	3-[3-trifluoromethylphenoxy]benzyl
204	10-undecenyl
205	4-cyclohexylbutyl
206	4-phenyl-2-fluorobenzyl
207	7-hexadecynyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
208	3-[cyclopentyl]propyl
209	4-[2-methylphenyl]benzyl
210	4-[phenylazo]benzyl
211	4-[4-flurophenyl]benzyl
212	3-nitro-4-[4-nitrophenyl]benzyl
213	3-nitro-4-[2-nitrophenyl]benzyl
214	9-decenyl
215	4-[3,4-dimethoxyphenyl]benzyl
216	4-[4-triflurometh ylphenyl]benzyl
217	5-hexenyl
218	4-[2-thienyl]benzyl
219	4-[6-phenylhexyloxy]benzyl
220	9,10-dihydro-2-phenantrene methyl
221	4-[3,4-dimethylphenyl]benzyl
222	4-[4-methylphenyl]-2-methylbenzyl
223	4-[3-phenylpropyloxy]benzyl
224	4-[3-methylphenyl]benzyl
225	4-[4-methylphenyl]-3-methylbenzyl
226	4-[4-pentenyloxy]benzyl
227	4-[1-heptynyl]benzyl
228	3-[4-t-butyl-phenylthio]benzyl
229	4-[4-chlorophenyl]benzyl
230	4-[4-bromophenyl]benzyl
231	4-[4-cyanophenyl]benzyl
232	4-[1-nonynyl]benzyl
233	4-[11-tridecynyloxy]benzyl
234	12-phenyldodecyl
235	6-phenyl-5-hexynyl
236	11-phenyl-10-undecynyl
237	4-[2-methylphenyl]-3-methylbenzyl
238	3-[2'-thienyl]-2-thienylmethyl
239	4-[benzyloxymethyl]cyclohexylmethyl
240	4-[4-chlorophenoxy]benzyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
241	4-[benzyl]cyclohexylmethyl
242	4-benzoylbenzyl
243	4-[phenoxymethyl]benzyl
244	4-[4-chlorobenzyl]benzyl

TABLE 2B

COMPOUND NO.	GLYCOPEPTIDE CORE	SIDECHAIN
180	vancomycin	1-napthylmethyl
181	vancomycin	4-phenylbenzyl
182	A82846A	4-phenylbenzyl
183	A82846C	4-phenylbenzyl
184	A82846C	4-phenoxybenzyl
185	PA-42867 A	4-phenylbenzyl
186	reduced A838450A	4-phenylbenzyl
187	alpha-avoparcin	4-phenylbenzyl
188	beta-avoparcin	4-phenylbenzyl

The formula I compounds have in vitro and in vivo activity against Gram-positive pathogenic bacteria. The minimal inhibitory concentrations (MIC) at which the formula I compounds inhibit certain bacteria are given in Table 3. The MIC's were determined using a standard broth micro-dilution assay.

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	vancomycin	A82846A	A82846B	A82846C	1	2	3	4	5	6
Staphylococcus aureus 446	0.5	0.25	0.25	0.5	≤0.06	≤0.06	≤0.06	≤0.06	1	0.5
Staphylococcus aureus 489	0.125	0.5	≤.06	≤.06	≤0.06	0.25	≤0.06	≤0.06	0.5	0.25
Staphylococcus aureus 447	0.5	0.25	0.25	0.5	≤0.06	≤0.06	≤0.06	0.25	0.5	0.5
Staphylococcus aureus X400	0.5	0.125	0.125	0.25	≤0.06	1	≤0.06	≤0.06	1	1
Staphylococcus aureus X778	0.5	0.125	0.125	0.5	0.125	≤0.06	≤0.06	≤0.06	0.5	0.25
Staphylococcus aureus 491	1	0.25	0.25	1	2	≤0.06	0.5	≤0.06	0.5	0.125
Staphylococcus aureus S13E	0.5	0.125	0.125	0.25	0.125	≤0.06	≤0.06	≤0.06	1	0.25
Staphylococcus aureus SA1199	0.5	0.125	0.125	0.25	≤0.06	0.5	0.125	≤0.06	1	0.25
Staphylococcus aureus SA1199A	0.125	≤.06	≤.06	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	0.5	≤.06	0.125	≤.06		≤0.06	≤0.06	≤0.06	≤0.06	
Staphylococcus haemolyticus 105	16	0.5	1	1	4	2	4	0.5	2	0.5
Staphylococcus haemolyticus 415	8	1	4	2	4	1	8	0.5	1	0.5
Staphylococcus epidermidis 270	16	0.25	0.25	0.125	8	8	8	≤0.06	0.25	0.125
Entercoccus faecium 180	>64	16	8	16	0.5	0.25	0.5	0.125	≤0.06	0.125
Entercoccus faecium 180-1	0.5	0.125	0.125	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	2	0.125	0.25	0.5	0.125	0.125	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 276	1	0.125	0.125	0.5	≤0.06	0.5	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus gallinarum 245	4	0.125	0.25	0.5	4	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Haemophilus influenzae RD	>64	>64	>64	>64	>64					>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.5			0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	0.25			≤.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	7	8	9	10	11	12	13	14	15	16	17
Staphylococcus aureus 446	8	2	2	16	4	32	2	4	1	4	2
Staphylococcus aureus 489	2	4	0.5	>64	1	8	1	2	≤0.06	0.5	1
Staphylococcus aureus 447	4	8	4	>64	4	32	8	8	2	4	8
Staphylococcus aureus X400	1	8	0.5	>64	0.5	8	1	4	0.25	0.5	0.5
Staphylococcus aureus X778	0.25	8	0.25	16	0.25	8	2	4	0.25	2	0.5
Staphylococcus aureus 491	2	4	0.5	16	1	4	2	1	0.25	1	2
Staphylococcus aureus S13E	2	8	0.5	8	0.5	8	0.25	4	0.5	1	1
Staphylococcus aureus SA1199	4	2	0.25	8	2	8	0.5	8	0.25	2	4
Staphylococcus aureus SA1199A	≤0.06	2	≤0.06	4	≤0.06	8	≤0.06	0.5	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	1		0.25	8	2		4	8	0.25	1	1
Staphylococcus haemolyticus 105	8	8	4	>64	4	16	8	4	0.5	8	8
Staphylococcus haemolyticus 415	16	8	4	>64	2	32	1	8	2	4	8
Staphylococcus epidermidis 270	4	4	16	>64	2	0.125	8	4	1	2	4
Entercoccus faecium 180	2	1	1	8	1	4	2	1	0.5	1	2
Entercoccus faecium 180-1	≤0.06	0.5	≤0.06	4	≤0.06	4	≤0.06	1	≤0.06	0.125	≤0.06
Entercoccus faecalis 2041	0.125	4	0.25	16	0.5	16	0.125	2	≤0.06	0.5	0.25
Entercoccus faecalis 276	1	4	0.26	18	1	4	0.5	4	≤0.06	2	0.5
Entercoccus gallinarum 245	0.5	8	0.25	8	≤0.06	32	0.25	0.25	≤0.06	1	0.5
Haemophilus influenzae RD	16	>64	≤0.06			64	32				32
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	0.5	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	18	19	20	21	22	23	24	25	26	27	28
Staphylococcus aureus 446	2	0.5	0.5	>64	16	38	0.5	0.5	0.25	2	0.25
Staphylococcus aureus 489	1	0.25	0.5	32	8	>64	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus 447	8	1	4	>64	16	16	1	0.25	2	8	1
Staphylococcus aureus X400	1	0.25	0.5	32	8	16	0.25	≤0.06	0.25	0.5	≤0.06
Staphylococcus aureus X778	0.5	0.25	0.25	32	8	16	0.125	≤0.06	0.125	0.5	≤0.06
Staphylococcus aureus 491	2	2	1	64	8	16	0.5	0.125	0.5	1	0.25
Staphylococcus aureus S13E	1	≤0.06	≤0.06	64	16	16	≤0.06	≤0.06	0.25	0.125	≤0.06
Staphylococcus aureus SA1199	2	0.5	2	64	16	16	0.5	≤0.06	1	0.5	0.125
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	16	4	16	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	2	1	0.5	64	16	16	2	0.125	0.5	1	0.125
Staphylococcus haemolyticus 105	16	4	8	>64	16	4	4	1	4	16	4
Staphylococcus haemolyticus 415	8	8	4	64	16	16	≤0.06	32	8	8	8
Staphylococcus epidermidis 270	8	2	2	32	4	64	1	0.5	1	4	1
Entercoccus faecium 180	2	1	1	8	1	>64	4	0.5	4	8	1
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	8	≤0.06	32	≤0.06	≤0.06	0.25	0.5	≤0.06
Entercoccus faecalis 2041	0.25	≤0.06	≤0.06	32	2	32	≤0.06	0.25	0.25	0.125	0.25
Entercoccus faecalis 276	1	≤0.06	0.25	64	4	32	0.25	0.25	≤0.06	0.5	≤0.06
Entercoccus gallinarum 245	1	≤0.06	0.25	8	1	8	0.25	≤0.06	0.125	0.5	0.25
Haemophilus influenzae RD	16	32	8	>64	64	>64	>64	32	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	2	≤0.06	1	≤0.06	≤0.06	≤0.06	≤0.06	
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	0.5	0.25	0.5	≤0.06	≤0.06	≤0.06	≤0.06	

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	29	30	31	32	33	34	35	36	37	38	39
Staphylococcus aureus 446	1	1	0.5	1	4	32	0.5	8	0.5	0.5	0.125
Staphylococcus aureus 489	1	0.125	≤0.06	1	≤0.06	8	≤0.06	2	0.125	≤0.06	≤0.06
Staphylococcus aureus 447	0.25	2	0.5	0.5	0.125	8	0.125	2	0.125	0.125	0.25
Staphylococcus aureus X400	0.25	≤0.06	0.125	0.5	0.25	32	0.25	4	0.25	1	≤0.06
Staphylococcus aureus X778	≤0.06	≤0.06	0.125	0.5	0.5	16	≤0.06	2	≤0.06	0.5	≤0.06
Staphylococcus aureus 491	0.25	0.5	0.5	0.25	0.125	8	0.125	1	0.25	0.5	0.25
Staphylococcus aureus S13E	1	0.125	0.25	1	≤0.06	16	≤0.06	2	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199	0.25	0.5	0.25	1	1	16	0.25	4	0.25	1	≤0.06
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	2	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	0.25	0.125	0.25	0.125	0.125	16	0.25	4	≤0.06	0.125	≤0.06
Staphylococcus haemolyticus 105	4	4	4	4	2	32	2	4	0.25	1	2
Staphylococcus haemolyticus 415	1	16	16	4	8	>64	4	8	1	1	4
Staphylococcus epidermidis 270	0.5	2	1	1	2	16	1	2	0.25	0.5	0.25
Entercoccus faecium 180	0.25	2	4	0.25	2	4	1	0.25	0.125	≤0.06	0.5
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	2	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	0.25	≤0.06	0.25	0.25	≤0.06	8	≤0.06	1	0.125	≤0.06	≤0.06
Entercoccus faecalis 276	0.25	0.25	0.25	0.125	≤0.06	16	≤0.06	2	1	0.5	≤0.06
Entercoccus gallinarum 245	0.25	≤0.06	0.25	0.25	0.25	4	≤0.06	0.25	0.125	0.125	≤0.06
Haemophilus influenzae RD	>64	>64	>64	>64							
Escherichia coli EC14	64	>64	>64	32	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203									≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1									≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	40	41	42	43	44	45	46	47	48	49	50
Staphylococcus aureus 446	4	2	1	0.5	0.25	1	1	0.125	0.125	0.5	0.5
Staphylococcus aureus 489	4	≤0.06	0.5	≤0.06	≤0.06	0.5	1	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus 447	2	0.25	0.5	2	1	16	2	2	2	1	0.5
Staphylococcus aureus X400	4	≤0.06	1	0.25	≤0.06	0.25	2	≤0.06	≤0.06	0.125	0.125
Staphylococcus aureus X778	4	0.125	1	≤0.06	≤0.06	0.25	2	≤0.06	≤0.06	≤0.06	0.125
Staphylococcus aureus 491	4	0.5	0.5	1	0.125	1	2	0.5	0.25	0.125	0.5
Staphylococcus aureus S13E	4	≤0.06	0.5	0.25	0.25	0.5	2	≤0.06	≤0.06	≤0.06	0.125
Staphylococcus aureus SA1199	4	≤0.06	1	0.5	0.25	2	2	0.5	0.25	2	1
Staphylococcus aureus SA1199A	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.5	0.25	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	8	0.25	2	0.5	0.25	1	2	0.25	1	1	2
Staphylococcus haemolyticus 105	2	2	2	4	2	16	2	4	2	1	0.5
Staphylococcus haemolyticus 415	2	4	1	8	4	8	2	16	8	1	1
Staphylococcus epidermidis 270	1	0.25	0.5	2	0.5	8	2	1	1	1	0.5
Entercoccus faecium 180	1	0.25	0.25	4	8	1	0.5	2	1	0.25	0.25
Entercoccus faecium 180-1	2	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	1	≤0.06	0.125	0.5	≤0.06	0.125	1	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 276	2	≤0.06	8	0.5	0.125	0.25	0.5	≤0.06	≤0.06	0.25	0.25
Entercoccus gallinarum 245	11	≤0.06	1	0.5	0.5	0.5	0.25	16	1	1	1
Haemophilus influenzae RD					>64	>64	>64	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06							
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06		≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	51	52	53	54	55	56	57	58	59	60	61
Staphylococcus aureus 446	0.25	≤0.06	2	1	0.5	0.5	0.25	0.25	0.5	1	0.5
Staphylococcus aureus 489	≤0.06	0.5	2	≤0.06	1	1	0.5	≤0.06	0.125	0.5	1
Staphylococcus aureus 447	0.5	≤0.06	4	0.25	4	2	0.5	1	1	2	2
Staphylococcus aureus X400	≤0.06	≤0.06	4	≤0.06	≤0.06	≤0.06	0.125	≤0.06	0.25	0.5	≤0.06
Staphylococcus aureus X778	0.5	0.5	2	≤0.06	0.5	0.125	≤0.06	≤0.06	≤0.06	0.25	0.125
Staphylococcus aureus 491	0.25		2		0.5	0.5		0.125		1	0.5
Staphylococcus aureus S13E	0.5	0.5	2	0.5	0.5	0.125	≤0.06	≤0.06	0.125	0.25	0.125
Staphylococcus aureus SA1199	0.5	2	2	0.5	0.5	0.5	1	1	≤0.06	0.5	0.25
Staphylococcus aureus SA1199A	≤0.06	≤0.06	1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	1	2	2	1	0.5	0.5	0.125	0.125	0.5	0.5	0.25
Staphylococcus haemolyticus 105	0.5	0.5	2	2	4	4	8	4	8	>64	64
Staphylococcus haemolyticus 415	1	1	2	1	16	16	1	8	8	16	8
Staphylococcus epidermidis 270	0.5	0.5	2	0.25	1	1	0.5	4	1	2	1
Entercoccus faecium 180	0.5	2	1	1	2	2	0.5	8	8	4	2
Entercoccus faecium 180-1	≤0.06	≤0.06	2	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	≤0.06	0.5	1	≤0.06	0.125	0.25	≤0.06	0.5	0.5	0.25	≤0.06
Entercoccus faecalis 276	≤0.06	0.125	8	1	0.5	0.25	0.5	0.5	0.125	0.5	0.25
Entercoccus gallinarum 245	1	1	2	0.5	16	16	2	0.5	1	16	8
Haemophilus influenzae RD	>64	>64	>64		>64	>64	>64	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203		≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06		
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	62	63	64	65	66	67	68	69	70	71	72
Staphylococcus aureus 446	2	0.5	0.25	2	0.25	0.25	0.125	1	0.125	4	2
Staphylococcus aureus 489	2	8	0.25	0.125	1	≤0.06	0.125	0.25	≤0.06	0.25	≤0.06
Staphylococcus aureus 447	0.5	1	0.5	1	1	1	0.25	1	0.5	4	1
Staphylococcus aureus X400	≤0.06	≤0.06	0.125	0.125	0.125	1	≤0.06	0.5	≤0.06	1	0.125
Staphylococcus aureus X778	0.5	0.125	2	0.5	≤0.06	0.25	≤0.06	0.125	≤0.06	2	0.25
Staphylococcus aureus 491	0.125	0.5	0.125	0.5	0.25	1	0.125	1	0.5	2	0.25
Staphylococcus aureus S13E	0.5	0.125	2	0.5	≤0.06	0.25	≤0.06	0.25	≤0.06	1	≤0.06
Staphylococcus aureus SA1199	0.25	0.25	1	0.5	0.25	1	≤0.06	1	≤0.06	1	1
Staphylococcus aureus SA1199A	≤0.06	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06
Staphylococcus aureus SA1199B	1	0.5	0.125	2	0.25	1	0.5	2	≤0.06	4	≤0.06
Staphylococcus haemolyticus 105	2	4	64	64	64	64	2	4	2	16	1
Staphylococcus haemolyticus 415	4	8	2	4	8	2	4	8	2	8	4
Staphylococcus epidermidis 270	1	1	0.5	1	1	0.5	2	2	0.25	2	0.25
Entercoccus faecium 180	4	16	0.125	0.5	2	0.25	2	4	0.5	4	0.5
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06
Entercoccus faecalis 2041	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06	1	≤0.06
Entercoccus faecalis 276	0.5	0.5	0.5	0.5	≤0.06	≤0.06	≤0.06	0.5	≤0.06	2	≤0.06
Entercoccus gallinarum 245	4	8	2	4	8	2	4	8	2	8	4
Haemophilus influenzae RD	>64	>64	>64	>64	>64	>64	>64	>64	16	>64	32
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06									
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06					

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	73	74	75	76	77	78	79	80	81	82	83
Staphylococcus aureus 446	0.25	4	2	0.25	≤0.06	2	2	4	2	2	1
Staphylococcus aureus 489	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	2	2	2	0.25	0.25
Staphylococcus aureus 447	0.25	1	1	0.5	1	≤0.06	2	2	2	4	2
Staphylococcus aureus X400	0.5	≤0.06	≤0.06	0.25	≤0.06	≤0.06	0.25	4	1	0.25	2
Staphylococcus aureus X778	1	≤0.06	≤0.06	0.25	≤0.06	≤0.06	2	0.5	1	0.5	0.5
Staphylococcus aureus 491	0.25	0.125	0.25	0.25		0.25	4	1	1	1	0.5
Staphylococcus aureus S13E		0	0		0.125		4	1	0.5	≤0.06	0.125
Staphylococcus aureus SA1199	0.5	≤0.06	2	≤0.06	≤0.06	0.125	1	2	2	0.25	2
Staphylococcus aureus SA1199A	0.25	≤0.06	≤0.06	0.125	≤0.06	≤0.06	0.125	1	0.5	0.5	0.25
Staphylococcus aureus SA1199B	≤0.06	1	0.5	0.25	0.125	≤0.06	1	1	1	1	1
Staphylococcus haemolyticus 105	0.5	4	2	2	2	2	4	4	1	8	2
Staphylococcus haemolyticus 415	2	4	4	4	8	16	4	4	4	8	4
Staphylococcus epidermidis 270	0.125	0.5	0.5	0.25	0.5	0.5	0.5	2	1	4	2
Entercoccus faecium 180	0.5	0.5	0.5	0.5	8	1	≤0.06	0.125	≤0.06	2	8
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	0.125	≤0.06	≤0.06	≤0.06	0.125	0.125	0.125
Entercoccus faecalis 2041	0.125	≤0.06	≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	0.5	0.5
Entercoccus faecalis 276	0.25		≤0.06	≤0.06	0.25	0.125	≤0.06	≤0.06	≤0.06	≤0.06	
Entercoccus gallinarum 245	2	≤0.06	4	4	0.25	0.125	≤0.06	≤0.06	0.25	0.125	0.5
Haemophilus influenzae RD	0.25	0.5	2	>64	64		16	16	16	64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	84	85	86	87	88	89	90	91	92	93	94
Staphylococcus aureus 446	0.5	0.125	1	1	0.25	0.5	2	0.5	2	2	1
Staphylococcus aureus 489	≤0.06	0.25	1	0.5	0.5	0.25	2	≤0.06	≤0.06	0.25	2
Staphylococcus aureus 447	4	0.125	0.5	0.5	0.25	1	1	0.5	0.5	0.25	0.5
Staphylococcus aureus X400	≤0.06	0.25	1	1	≤0.06	0.25	1	0.5	0.5	≤0.06	1
Staphylococcus aureus X778	≤0.06	0.25	1	2	0.5	0.25	1	≤0.06	0.25	1	0.5
Staphylococcus aureus 491	1	0.125	1	2	0.5	1	2	1	1	0.25	0.5
Staphylococcus aureus S13E	0.125	0.5	1	0.5	1	0.25	1	≤0.06	0.125	1	2
Staphylococcus aureus SA1199	0.25	0.5	0.5	2	1	0.5	2	≤0.06	1	2	0.5
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.5	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	0.5	1	1	0.5	1	1	1	0.5	0.5	1	2
Staphylococcus haemolyticus 105	8	1	1	1	1	1	2	2	2	1	2
Staphylococcus haemolyticus 415	16	2	1	2	2	2	2	2	2	1	2
Staphylococcus epidermidis 270	1	0.5	1	1	1	1	1	0.5	1	1	1
Entercoccus faecium 180	4	≤0.06	≤0.06	≤0.06	0.125	0.125	0.25	0.5	0.125	≤0.06	0.25
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.125	≤0.06	0.125	≤0.06	≤0.06
Entercoccus faecalis 276		0.125	≤0.06	≤0.06	≤0.06	≤0.06	2	≤0.06	0.125	0.25	0.125
Entercoccus gallinarum 245	0.25	2	1	2	≤0.06	≤0.06	2	2	2	1	2
Haemophilus influenzae RD							>64				
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	95	96	97	98	99	100	101	102	103	104	105
Staphylococcus aureus 446	0.5	1	1	0.5	0.5	1	0.5	1	0.5	≤0.06	0.25
Staphylococcus aureus 489	2	1	0.25	≤0.06	0.25	0.5	≤0.06	≤0.06	≤0.06	≤0.06	0.5
Staphylococcus aureus 447	0.5	1	1	0.25	2	0.5	1	1	1	0.25	0.5
Staphylococcus aureus X400	1	2	1	≤0.06	0.125	1	≤0.06	≤0.06	≤0.06	≤0.06	0.5
Staphylococcus aureus X778	1	1	0.25	≤0.06	0.5	1	0.25	≤0.06	0.5	≤0.06	0.5
St [illegible]ylococcus aureus 491	1	1	0.5	0.25	1	≤0.06	0.5	1	1	≤0.06	0.25
Staphylococcus aureus S13E	2	1	>64	0.5	0.5	1	0.25	1	1	≤0.06	0.5
Staphylococcus aureus SA1199	0.5	2	2	0.5	0.5	0.5	0.25	0.125	1	2	1
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	≤0.06	0.5	0.125	0.5	≤0.06	≤0.06	≤0.06	0.25
Staphylococcus aureus SA1199B	1	1	1	1	0.5	0.5	1	1	2	0.125	0.5
Staphylococcus haemolyticus 105	1	2	2	1	8	1	1	2	4	2	1
Staphylococcus haemolyticus 415	1	2	2	1	32	2	8	4	8	2	1
Staphylococcus epidermidis 270	1	2	1	≤0.06	1	0.5	0.5	1	1	0.25	0.25
Entercoccus faecium 180	0.5	0.5								≤0.06	0.25
Entercoccus faecium 180-1	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	≤0.06	1	≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25
Entercoccus faecalis 276	0.125	0.5	≤0.06	0.125	0.25	0.25	0.125	0.25	0.25	≤0.06	0.25
Entercoccus gallinarum 245	1	2	2	1	32	2	8	4	8	2	1
Haemophilus influenzae RD					>64	>64	>64			32	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	106	107	108	109	110	111	112	113	114	115	116
Staphylococcus aureus 446	2	2	2	1	0.5	2	2	≤0.06	0.5	0.125	0.5
Staphylococcus aureus 489	2	1	0.25	≤0.06	1	1	0.25	0.125	1	0.125	1
Staphylococcus aureus 447	0.25	1	0.5	1	1	1	1	0.25	0.5	0.5	1
Staphylococcus aureus X400	1	1	2	≤0.06	1	1	1	0.125	2	1	1
Staphylococcus aureus X778	1	0.5	0.125	≤0.06	0.5	2	1	1	2	1	2
Staphylococcus aureus 491	0.5	1	0.25	0.25	0.25	2	1	0.25	1	0.5	0.5
Staphylococcus aureus S13E	1	2	1	0.25	1	1	1	≤0.06	2	0.25	1
Staphylococcus aureus SA1199	1	1	2	≤0.06	0.25	2	2	1	2	0.125	4
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.5	0.125	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	2	2	2	0.5	0.5	1	0.5	≤0.06	1	0.25	0.5
Staphylococcus haemolyticus 105	1	2	2	1	4	1	2	4	2	1	2
Staphylococcus haemolyticus 415	1	2	1	4	2	4	2	1	2	2	4
Staphylococcus epidermidis 270	0.25	0.5	0.125	0.25	2	1	1	0.25	1	0.5	1
Entercoccus faecium 180	≤0.06	0.125	0.125	0.25	0.25	≤0.06	≤0.06	≤0.06	≤0.06	1	≤0.06
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	0.125	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06	≤0.06
Entercoccus faecalis 276	0.5	1	0.5	≤0.06	0.5	0.5	0.5	0.25	1	0.125	0.25
Entercoccus gallinarum 245	1	2	≤0.06	≤0.06	2	4	2	1	2	2	4
Haemophilus influenzae RD	>64	>64	>64	32	>64	>64	>64	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64		>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06		≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06		≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	117	118	119	120	121	122	123	124	125	126	127
Staphylococcus aureus 446	0.5	1	2	2	2	1	2	4	4	2	1
Staphylococcus aureus 489	0.125	0.25	0.5	2	1	≤0.06	2	0.25	2	0.25	2
Staphylococcus aureus 447	0.5	0.25	2	1	0.5	0.25	1	0.25	2	1	2
Staphylococcus aureus X400	≤0.06	0.25	1	0.25	0.125	≤0.06	1	1	1	1	2
Staphylococcus aureus X778	0.25	0.5	2	0.125	0.5	≤0.06	1	0.5	2	0.5	1
Staphylococcus aureus 491	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.125	1	0.25	1
Staphylococcus aureus S13E	≤0.06	0.25	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	1	0.5	2
Staphylococcus aureus SA1199	≤0.06	2	2	1	1	≤0.06	2	1	0.5	0.125	2
Staphylococcus aureus SA1199A	≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06	0.125	≤0.06	0.25	0.25	0.25
Staphylococcus aureus SA1199B	0.5	≤0.06	0.5	0.125	0.25	≤0.06	0.5	≤0.06	2	1	2
Staphylococcus haemolyticus 105	1	1	2	2	2	1	2	2	4	0.5	2
Staphylococcus haemolyticus 415	2	1	2	2	2	1	1	1	2	2	4
Staphylococcus epidermidis 270	0.5	1	2	2	1	≤0.06	1	0.25	1	1	≤0.06
Entercoccus faecium 180	1	0.125	0.125	≤0.06	≤0.06	≤0.06	0.25	≤0.06	1	1	≤0.06
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	<0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≥0.06	≤0.06	≤0.06
Entercoccus faecalis 276	0.25	≤0.06	0.125	≤0.06	≤0.06	≤0.06	0.25	≤0.06	2	1	≤0.06
Entercoccus gallinarum 245	2	1	2	2	2	1	1	1	12	2	4
Haemophilus influenzae RD		16	16	16	16	16	16	16			>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	128	129	130	131	132	133	134	135	136	137	138
Staphylococcus aureus 446	4	2	1	2	1	2	2	1	≤0.06	0.25	0.125
Staphylococcus aureus 489	1	≤0.06	0.5	1	1	1	0.5	0.125	≤0.06	≤0.06	≤0.06
Staphylococcus aureus 447	1	1	1	1	2	1	1	1	2	4	2
Staphylococcus aureus X400	1	0.25	0.5	1	1	0.5	0.25	≤0.06	≤0.06	≤0.06	≤0.0606
Staphylococcus aureus X778	1	0.25	1	0.5	2	2	1	1	≤0.06	≤0.06	0.25
Staphylococcus aureus 491	2	0.5	0.5	0.125	0.5	0.25	0.5	0.25	0.25	0.25	0.125
Staphylococcus aureus S13E	1	0.25	0.5	1	2	1	2	1	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199	0.5	0.25	1	0.25	1	0.25	0.25	1	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199A	0.5	≤0.06	≤0.06	≤0.06	0.25	0.25	0.25	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	2	0.25	2	1	2	2	2	0.25	≤0.06	≤0.06	0.5
Staphylococcus haemolyticus 105	1	4	1	1	1	2	2	0.5	2	2	4
Staphylococcus haemolyticus 415	2	4	2	2	2	2	4	2	4	8	8
Staphylococcus epidermidis 270	1	1	1	1	2	1	2	0.5	1	0.5	2
Entercoccus faecium 180	1	4	1	≤0.06	0.25	1	0.5	1	2	0.125	4
Entercoccus faecium 180-1	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	0.5	≤0.06	0.125	≤0.06	1	0.25	0.25	0.125	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 276	1	0.125	1	0.25	1	1	1	0.5	≤0.06	≤0.06	≤0.06
Entercoccus gallinarum 245	2	0.125	2	2	2	2	4	2	4	8	0.125
Haemophilus influenzae RD		>64									
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	139	140	141	142	143	144	145	146	147	148	149
Staphylococcus aureus 446	0.5	0.125	2	2	0.5	16	0.5	0.5	0.5	1	0.5
Staphylococcus aureus 489	0.25	≤0.06	0.25	0.5	≤0.06	4	≤0.06	0.25		0.25	≤0.06
Staphylococcus aureus 447	1	0.25	1	2	4	16	1	2	0.125	1	4
Staphylococcus aureus X400	0.25	≤0.06	0.25	1	0.125	8	0.25	0.5	4	≤0.06	≤0.06
Staphylococcus aureus X778	0.125	0.25	0.5	1	≤0.06	8	0.125	≤0.06	0.25	2	0.5
Staphylococcus aureus 491	0.5	0.25	0.5	0.5	0.5	8	0.5	1	≤0.06	0.125	0.5
Staphylococcus aureus S13E	≤0.06	≤0.06	0.25	2	0.125	8	0.125	0.5	1	1	0.25
Staphylococcus aureus SA1199	0.125	≤0.06	0.25	1	0.125	8	0.25	≤0.06	0.5	2	0.25
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	2	≤0.06	≤0.06	0.25	≤0.06	≤0.06
Staphylococcus aureus SA1199B	2	≤0.06	2	2	0.25	8	≤0.06	≤0.06	≤0.06	0.5	1
Staphylococcus haemolyticus 105	4	2	1	1	8	64	2	2	1	1	4
Staphylococcus haemolyticus 415	8	8	4	1	32	>64	8	4	8	2	16
Staphylococcus epidermidis 270	1	0.25	1	0.25	1	16	1	2	16	0.5	1
Entercoccus faecium 180	2	1	0.5	0.5	4	8	4	8	2	0.25	1
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	4	≤0.06	≤0.06	2	≤0.06	≤0.06
Entercoccus faecalis 2041	≤0.06	≤0.06	≤0.06	≤0.06	0.125	8	0.25	0.5	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 276	1	0.5	0.5	1	0.25	8	0.125	1	0.125	≤0.06	≤0.06
Entercoccus gallinarum 245	8	8	4	1	32	4	0.25	0.5	0.125	2	16
Haemophilus influenzae RD								>64			
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	150	151	152	153	154	155	156	157	158	159	160
Staphylococcus aureus 446	1	2	2	0.5	2	2	2	0.5	2	0.5	2
Staphylococcus aureus 489	0.5	≤0.06	0.5	1	1	0.5	1	0.5	2	0.25	0.21
Staphylococcus aureus 447	0.5	1	8	0.5	2	8	1	0.25	4	4	1
Staphylococcus aureus X400	≤0.06	≤0.06	1	0.5	2	1	2	0.5	4	4	4
Staphylococcus aureus X778	2	1	0.5	0.5	0.5	≤0.06	1	0.25	4	2	4
Staphylococcus aureus 491	≤0.06	0.5	1	0.125	0.5	1	1	≤0.06	1	2	0.125
Staphylococcus aureus S13E	0.25	0.25	0.5	0.125	0.25	1	1	0.25	2	1	1
Staphylococcus aureus SA1199	1	0.125	1	0.5	2	1	1	1	4	0.125	0.25
Staphylococcus aureus SA1199A	≤0.06	≤0.06	0.25	≤0.06	0.125	≤0.06	≤0.06	≤0.06	1	≤0.06	0.125
Staphylococcus aureus SA1199B	0.5	0.25	0.5	0.25	0.25	1	0.5	1	4	≤0.06	≤0.06
Staphylococcus haemolyticus 105	1	1	16	2	4	16	4	1	4	16	8
Staphylococcus haemolyticus 415	2	4	16	1	4	16	2	1	8	8	8
Staphylococcus epidermidis 270	0.25	0.5	4	0.25	0.5	1	1	0.25	4	0.5	1
Entercoccus faecium 180	0.25	0.25	4	0.125	1	4	1	≤0.06	0.25	2	0.5
Entercoccus faecium 180-1	≤0.06	≤0.06	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06	≤0.06
Entercoccus faecalis 2041	≤0.06	≤0.06	0.125	≤0.06	0.125	0.125	0.5	≤0.06	1	0.125	≤0.06
Entercoccus faecalis 276	1	≤0.06	0.25	0.5	0.5	0.25	2	≤0.06	2	0.125	2
Entercoccus gallinarum 245	2	4	16	1	4	16	2	1	8	8	8
Haemophilus influenzae RD						16	2				
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	161	162	163	164	165	166	167	168	169	170	171
Staphylococcus aureus 446	0.5	0.5	1	2	1	2	1	≤0.06	0.25	2	1
Staphylococcus aureus 489	≤0.06	0.25	8	2	2	2	16	0.125	≤0.06	0.25	0.5
Staphylococcus aureus 447	1	≤0.06	0.5	2	0.5	2	4	≤0.06	2	0.5	1
Staphylococcus aureus X400	0.5	≤0.06	0.5	0.5	0.5	1	1	≤0.06	≤0.06	0.5	≤0.06
Staphylococcus aureus X778	0.5	≤0.06	2	1	0.125	1	16	0.5	≤0.06	1	≤0.06
Staphylococcus aureus 491	0.5	0.25	≤0.06	1	0.5	0.5	2	0.5	0.25	0.5	0.25
Staphylococcus aureus S13E	0.125	≤0.06	1	4	≤0.06	4	4	≤0.06	≤0.06	0.25	≤0.06
Staphylococcus aureus SA1199	0.25	≤0.06	2	2	0.25	2	2	0.5	≤0.06	1	0.25
Staphylococcus aureus SA1199A	≤0.06	≤0.06	0.5	0.[illegible]	≤0.06	0.125	4	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	0.25	≤0.06	1	2	1	2	4	1	0.125	0.25	0.25
Staphylococcus haemolyticus 105	4	0.25	8	2	4	2	32	0.5	2	4	4
Staphylococcus haemolyticus 415	8	2	8	2	4	2	16	2	4	4	8
Staphylococcus epidermidis 270	1	≤0.06	4	1	1	0.5	8	0.125	0.25	1	1
Entercoccus faecium 180	2	≤0.06	1	0.5	0.5	0.25	2	0.25	1	2	1
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	≤0.06	≤0.06	1	1	≤0.06	≤0.06	8	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 276	0.125	≤0.06	1	1	0.5	0.5	4	0.125	≤0.06	0.5	0.125
Entercoccus gallinarum 245	8	2	8	2	4	2	16	2	4	4	8
Haemophilus influenzae RD										>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	172	173	174	175	176	177	178	179	180	181	182
Staphylococcus aureus 446	4	4	0.5	1	2	0.5	1	0.125	0.125	≤0.06	2
Staphylococcus aureus 489	0.5	2	≤0.06	0.25	0.5	≤0.06	0.125	≤0.06	≤0.06	≤0.06	2
Staphylococcus aureus 447	0.5	4	4	1	1	4	0.5	0.25	0.125	≤0.06	0.25
Staphylococcus aureus X400	0.5	4	≤0.06	0.125	1	≤0.06	0.125	≤0.06	≤0.06	≤0.06	1
Staphylococcus aureus X778	2	4	≤0.06	0.5	1	2	1	≤0.06	≤0.06	≤0.06	2
Staphylococcus aureus 491	0.5	2	1	0.5	2	0.5	0.125	0.125	0.5		1
Staphylococcus aureus S13E	≤0.06	4	≤0.06	0.25	2	0.25	0.5	0.25	≤0.06	≤0.06	0.25
Staphylococcus aureus SA1199	1	2	≤0.06	≤0.06	2	0.25	1	1	0.125	≤0.06	2
Staphylococcus aureus SA1199A	≤0.06	0.5	≤0.06	0.5	>64	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	≤0.06	4	0.125	≤0.06	1	0.25	1	0.125	≤0.06	≤0.06	4
Staphylococcus haemolyticus 105	0.25	2	4	2	4	4	1	0.5	2	0.25	2
Staphylococcus haemolyticus 415	2	4	16	4	2	16	2	1	2	1	4
Staphylococcus epidermidis 270	0.5	2	2	0.5	0.5	1	0.25	0.25	0.125	0.125	0.25
Entercoccus faecium 180	0.5	0.5	2	1	2	4	0.25	≤0.06	8	4	2
Entercoccus faecium 180-1	≤0.06	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.125	≤0.06	≤0.06
Entercoccus faecalis 2041	≤0.06	0.5	≤0.06	≤0.06	0.125	0.25	≤0.06	≤0.06	0.25	0.125	1
Entercoccus faecalis 276	0.125	2	≤0.06	≤0.06	2	0.25	0.5	≤0.06	2	2	1
Entercoccus gallinarum 245	2	4	16	4	2	16	2	1	0.25	≤0.06	1
Haemophilus influenzae RD	32	>64	>64	16	8	>64	4	4		32	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	0.5	0.25	16	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	0.5	0.25	8	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	183	184	185	186	189	190	191	192	193	194	195
Staphylococcus aureus 446	≤0.06	2	≤.06	≤.06	0.5	0.25	2	0.5	0.5	≤0.06	0.5
Staphylococcus aureus 489	≤0.06	≤.06	≤.06	≤.06	1	0.125	2	1	0.125	0.125	1
Staphylococcus aureus 447	≤0.06	≤.06	≤.06	≤.06	0.5	1	2	2	≤0.06	0.5	1
Staphylococcus aureus X400	≤0.06	0.5	≤.06	≤.06	0.125	≤0.06	1	1	0.25	≤0.06	2
Staphylococcus aureus X778	≤0.06	0.5	≤.06	≤.06	0.25	0.125	2	1	≤0.06	0.5	0.5
Staphylococcus aureus 491	0.125	0.5	≤.06	≤.06	≤0.06	0.125	1	0.5	≤0.06	≤0.06	0.5
Staphylococcus aureus S13E	≤0.06	1	≤.06	≤.06	0.5	0.125	2	1	≤0.06	≤0.06	2
Staphylococcus aureus SA1199	≤0.06	0.125	≤.06	≤.06	0.5	0.25	2	2	0.125	0.5	0.5
Staphylococcus aureus SA1199A	≤0.06	≤.06	≤.06	≤.06	≤0.06	≤0.06	0.5	0.25	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	≤0.06	1	≤.06	≤.06	1	0.5	2	0.5	0.125	0.125	1
Staphylococcus haemolyticus 105	≤0.06	0.25	≤.06	0.5	1	8	2	1	0.5	1	1
Staphylococcus haemolyticus 415	≤0.06	≤.06	≤.06	1	1	8	8	2	1	2	4
Staphylococcus epidermidis 270	≤0.06	4	≤.06	0.125	0.25	2	2	1	0.25	0.5	0.25
Entercoccus faecium 180	2	8	0.125	2	0.125	8	4	0.25	≤0.06	≤0.06	0.5
Entercoccus faecium 180-1	≤0.06	≤.06	≤.06	≤.06	≤0.06	≤0.06	0.25	0.125	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	≤0.06	1	≤.06	≤.06	≤0.06	≤0.06	1	0.125	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 276	0.125	0.5	≤.06	≤.06	0.25	0.125	4	0.5	≤0.06	0.125	0.25
Entercoccus gallinarum 245	0.5	4	≤.06	2	1	8	8	2	1	2	4
Haemophilus influenzae RD	>64	64	8		32	>64	>64	>64	>64	>64	32
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06		≤.06	≤.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06		≤.06	≤.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	196	197	198	199	200	201	202	203	204	205
Staphylococcus aureus 446	0.5	1	1	0.5	1	4	4	0.5	0.125	2
Staphylococcus aureus 489	1	2	0.125	2	0.25	8	4	0.5	0.25	0.5
Staphylococcus aureus 447	0.5	2	0.125	1	0.5	16	8	1	≤0.06	0.5
Staphylococcus aureus X400	0.5	2	0.5	2	1	4	4	1	0.125	0.5
Staphylococcus aureus X778	1	2	0.125	1	0.5	4	4	1	0.5	0.5
Staphylococcus aureus 491	0.25	1	≤0.06	0.5	0.125	4	8	1	≤0.06	0.5
Staphylococcus aureus S13E	1	2	0.125	0.5	0.5	8	4	2	0.5	0.5
Staphylococcus aureus SA1199	0.5	2	0.5	1	1	8	8	2	0.125	1
Staphylococcus aureus SA1199A	≤0.06	1	≤0.06	0.125	≤0.06	2	2	0.5		≤0.06
Staphylococcus aureus SA1199B	0.5	2	0.5	1	1	16	8	1	0.25	0.5
Staphylococcus haemolyticus 105	0.5	1	0.5	2	1	8	4	1	0.5	1
Staphylococcus haemolyticus 415	1	4	1	4	2	8	8	2	0.25	1
Staphylococcus epidermidis 270	0.25	0.5	0.25	0.5	0.25	4	4	0.5	≤0.06	0.125
Entercoccus faecium 180	0.5	0.5	≤0.06	0.5	0.25	0.5	0.5	0.125	0.25	0.5
Entercoccus faecium 180-1	≤0.06	0.25	≤0.06	≤0.06	≤0.06	0.5	0.5	≤0.06	0.125	≤0.06
Entercoccus faecalis 2041	≤0.06	0.25	≤0.06	≤0.06	≤0.06	1	1	0.25	≤0.06	0.25
Entercoccus faecalis 276	0.25	1	0.25	1	0.5	4	4	0.5	≤0.06	0.5
Entercoccus gallinarum 245	1	4	1	4	2	8	8	-2	0.25	1
Haemophilus influenzae RD	32	32	32	32	32	32	32	16	2	16
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	206	207	208	209	210	211	212	213	214	215
Staphylococcus aureus 446	0.5	8	1	1	2	1	≤0.06	≤0.06	1	0.5
Staphylococcus aureus 489	1	4	0.5	1	1	0.25	≤0.06	≤0.06	1	2
Staphylococcus aureus 447	0.5	8	1	1	0.5	0.5	0.25	0.25	2	0.5
Staphylococcus aureus X400	0.5	8	0.25	1	≤0.06	0.5	≤0.06	≤0.06	0.5	0.5
Staphylococcus aureus X778	0.5	8	0.125	1	1	1	≤0.06	≤0.06	1	≤0.06
Staphylococcus aureus 491	≤0.06	1	0.5	0.25	≤0.06	0.25	≤0.06	≤0.06	1	0.25
Staphylococcus aureus S13E	1	8	0.25	0.5	≤0.06	0.5	≤0.06	≤0.06	1	2
Staphylococcus aureus SA1199	0.5	8	0.5	0.25	0.5	0.5	≤0.06	≤0.06	0.5	≤0.06
Staphylococcus aureus SA1199A	≤0.06	4	≤0.06	≤0.06	≤0.06	0.125	≤0.06	≤0.06	0.5	0.5
Staphylococcus aureus SA1199B	1	16	0.5	0.5	0.125	1	≤0.06	≤0.06	1	1
Staphylococcus haemolyticus 105	0.5	8	0.25	0.5	1	0.5	1	0.5	1	2
Staphylococcus haemolyticus 415	1	1	2	1	1	0.5	1	2	2	1
Staphylococcus epidermidis 270	0.25	8	0.5	0.125	0.25	0.5	≤0.06	0.5	≤0.06	0.125
Entercoccus faecium 180	≤0.06	1	0.25	≤0.06	≤0.06	≤0.06	≤0.06	0.125	0.25	≤0.06
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	0.25	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.125	0.25
Entercoccus faecalis 276	≤0.06	0.25	0.125	0.25	≤0.06	≤0.06	≤0.06	≤0.06	0.25	2
Entercoccus gallinarum 245	1	1	2	1	1	≤0.06	1	2	2	64
Haemophilus influenzae RD			32	16	>64	>64	>64	32	32	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203			≤0.06	≤0.06	≤0.06	≤0.06				≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	216	217	218	219	220	221	222	223	224	225
Staphylococcus aureus 446	1	0.25	4	8	1	1		0.25	0.5	1
Staphylococcus aureus 489	1	≤0.06	1	8	0.5	0.25	0.125	1	0.25	2
Staphylococcus aureus 447	1	1	1	8	0.5	0.5	0.5	0.5	0.5	1
Staphylococcus aureus X400	1	≤0.06	0.25	8	0.5	0.5	0.125	1	0.125	1
Staphylococcus aureus X778	0.25	≤0.06	1	8	0.5	0.5	≤0.06	1	0.125	0.5
Staphylococcus aureus 491	1	0.25	0.5	4	≤0.06	0.125	0.125	0.125	0.125	1
Staphylococcus aureus S13E	1	≤0.06	32	8	0.5	0.5	≤0.06	0.5	0.25	1
Staphylococcus aureus SA1199	≤0.06	≤0.06	4	4	1	1	1	2	0.25	1
Staphylococcus aureus SA1199A	1	≤0.06	≤0.06	1	≤0.06	≤0.06	0.125	≤0.06	≤0.06	0.25
Staphylococcus aureus SA1199B	0.5	0.125	0.25	8	0.5	1	0.125	1	0.5	2
Staphylococcus haemolyticus 105	0.5	2	0.5	2	0.5	1	1	1	1	0.5
Staphylococcus haemolyticus 415	0.25	8	4	2	0.5	2	1	1	0.5	4
Staphylococcus epidermidis 270	0.125	0.5	1	4	1	0.125	0.5	0.5	0.25	1
Entercoccus faecium 180	≤0.06	2	≤0.06	1	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	0.25	≤0.06	0.25	2	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.125
Entercoccus faecalis 276	0.5	≤0.06	≤0.06	2	0.125	0.25	≤0.06	0.125	≤0.06	0.25
Entercoccus gallinarum 245	64	8	≤0.06	2	0.5	2	1	1	0.5	4
Haemophilus influenzae RD	>64	>64	>64	32	>64	32	32	>64	32	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	226	227	228	229	230	231	232	233	234	235
Staphylococcus aureus 446	1	2	4	1	0.25	0.25	4	4	4	0.5
Staphylococcus aureus 489	0.5	2	2	1	0.25	≤0.06	8	4	4	0.5
Staphylococcus aureus 447	0.5	2	4	2	0.5	0.25	16	16	8	0.25
Staphylococcus aureus X400	0.25	1	1	1	0.5	≤0.06	8	8	8	0.125
Staphylococcus aureus X778	0.25	4	4	1	0.25	≤0.06	8	8	4	0.5
Staphylococcus aureus 491	0.25	2	1	0.5	0.125	≤0.06	4	8	8	0.125
Staphylococcus aureus S13E	0.5	4	8	1	0.5	≤0.06	8	8	8	0.125
Staphylococcus aureus SA1199	1	4	4	1	0.25	≤0.06	16	32	8	0.25
Staphylococcus aureus SA1199A	0.125	0.6	≤0.06	≤0.06	≤0.06	≤0.06	2	4	2	≤0.06
Staphylococcus aureus SA1199B	1	4	4	1	0.25	≤0.06	32	16	8	0.5
Staphylococcus haemolyticus 105	2	2	2	1	1	≤0.06	2	>64	8	0.5
Staphylococcus haemolyticus 415	1	4	4	2	2	0.5	32	>64	16	1
Staphylococcus epidermidis 270	1	2	2	0.5	0.5	0.125	8	8	4	0.5
Entercoccus faecium 180	≤0.06	0.25	1	≤0.06	≤0.06	≤0.06	0.5	2	1	0.5
Entercoccus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	1	2	1	≤0.06
Entercoccus faecalis 2041	≤0.06	0.25	0.25	≤0.06	≤0.06	≤0.06	2		0.5	≤0.06
Entercoccus faecalis 276	0.25	0.5	1	0.25	≤0.06	≤0.06	8	8	4	0.125
Entercoccus gallinarum 245	1	4	4	2	2	0.5	32	>64	16	1
Haemophilus influenzae RD	32	>64	>64	2	32	32	16	>64	>64	8
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	0.125	≤0.06	≤0.06	≤0.06	≤0.06			≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.5	0.25	≤0.06

TABLE 3
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

Organism	236	237	238	239	240	241
Staphylococcus aureus 446	1	2	1	1	1	0.5
Staphylococcus aureus 489	4	0.5	0.5	0.5	1	0.5
Staphylococcus aureus 447	4	1	0.5	0.5	0.5	1
Staphylococcus aureus X400	2	1	1	0.25	0.25	0.5
Staphylococcus aureus X778	2	0.5	0.5	0.25	0.5	1
Staphylococcus aureus 491	4	0.25	0.25	0.25	0.25	0.25
Staphylococcus aureus S13E	4	0.25	0.125	0.5	0.5	0.25
Staphylococcus aureus SA1199	4	1	0.5	0.5	0.5	1
Staphylococcus aureus SA1199A	2	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	4	0.25	0.5	0.5	0.25	1
Staphylococcus haemolyticus 105	4	1	0.5	1	1	1
Staphylococcus haemolyticus 415	4	1	2	1	2	1
Staphylococcus epidermidis 270	2	0.5	0.5	0.25	0.25	0.5
Entercoccus faecium 180	1	0.25	0.125	≤0.06	≤0.06	≤0.06
Entercoccus faecium 180-1	1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 2041	1	0.125	≤0.06	≤0.06	≤0.06	≤0.06
Entercoccus faecalis 276	2	1	≤0.06	0.25	0.5	≤0.06
Entercoccus gallinarum 245	4	1	≤0.06	1	2	≤0.06
Haemophilus influenzae RD	32	8	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06			≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

The formula I compounds have also shown in vivo antimicrobial activity against experimentally-induced infections in laboratory animals. When two doses of test compound were administered to mice experimentally infected with the test organism, the activity observed was measured as an ED_{50} value (effective dose in mg/kg to protect 50% of the test animals: see W. Wick et al., J. Bacteriol. 81, 233-235 (1961)). ED_{50} values observed for illustrative compounds are given in Table 4.

TABLE 4

In Vivo Activity of Formula I Compounds ED50 (mg/kg/2)			
Compound	Stapylococcus aureus	Streptococcus pyogenes	Streptococcus pneumoniae
vancomycin	1.2	0.8	1.1
A82846A	0.19	0.084	0.39
A82846B	0.25	0.12	0.18
A82846C	1.3	1.5	4.6
1	0.086	0.052	0.025
2	0.27	0.014	0.025
4	0.36	0.012	0.036
5	0.13	0.039	0.036
6	0.15	0.013	0.021
8	0.12	>0.5	0.273
12	0.13	>0.5	>0.5
14	0.43	0.37	>0.5
22	0.049	>0.5	>.05
25	0.16	0.087	0.088
29	0.088	0.1	0.054
32	0.055	0.034	0.039
36	0.19	0.28	0.31
39	0.1	0.045	<0.031
41	n.d.	0.082	0.087
46	n.d.	0.378	0.156
49	0.053	0.045	<0.031
50	0.1	0.047	0.057
51	0.16	0.057	0.036
52	0.052	0.046	0.074
53	0.077	0.16	0.071
57	0.041	0.054	0.046
64	n.d.	0.044	<0.031
87	n.d.	0.054	0.027
90	n.d.	0.058	0.049
93	n.d.	0.074	0.012
94	n.d.	0.16	0.049
97	n.d.	0.066	0.038
100	n.d.	0.062	0.046
104	n.d.	0.12	0.041
105	n.d.	0.12	0.041
106	n.d.	0.2	0.036
107	n.d.	0.27	0.092
108	n.d.	0.046	0.041
111	n.d.	0.099	0.084
114	n.d.	0.091	0.76
116	n.d.	0.89	0.058
118	n.d.	0.91	0.046
119	n.d.	0.16	0.08
120	n.d.	0.058	0.005
121	n.d.	0.041	0.047

TABLE 4

In Vivo Activity of Formula I Compounds ED50 (mg/kg/2)			
Compound	Stapylococcus aureus	Streptococcus pyogenes	Streptococcus pneumoniae
122	n.d.	0.23	0.31
123	n.d.	0.076	0.039
124	n.d.	0.092	0.041
131	n.d.	<0.031	0.077
204	n.d.	<0.031	0.046
211	n.d.	<0.031	0.041
223	n.d.	<0.031	<0.031
229	n.d.	0.058	0.078
230	n.d.	0.046	0.078
n.d. = not done			

One important aspect of the antimicrobial activity of many of the formula I compounds is their activity against vancomycin-resistant enterococci. This activity is illustrated in Table 5, which summarizes a comparison of the activity of illustrative compounds against representative vancomycin-resistant and vancomycin-susceptible enterococci (*Enterococcus faecium* and *Enterococcus faecalis*, mean geometric MIC (mcg/mL)), as determined using the standard broth micro-dilution assay. End points were read after 24-hour incubation. Modification of the amino sugar of the disaccharide moiety provides improved activity against vancomycin-resistant strains over the parent glycopeptide antibiotic.

TABLE 5

Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
vancomycin	282	3.9
A82846A	>64	1.7
A82846B	29	0.22
A82846C	353	1.3
1	0.25	0.0061
2	0.044	0.00038
3	2.8	0.11
4	0.50	0.062
5	0.50	0.072
6	1.2	0.14
7	2.8	0.43
8	1.0	0.57
9	11	0.38
10	3.4	3.5
11	6.7	0.22
12	1.7	1.1
13	19	0.76
14	0.50	0.76
15	6.7	0.14
16	9.5	0.67
17	9.5	0.38
18	6.7	0.38
19	4.8	0.22
20	4.8	0.38
21	5.7	4.3
22	1.0	1.5
23	5.7	2.0
24	54	0.67
25	4.0	0.22
26	54	0.66
27	45	1.5
28	4.7	0.71
29	0.21	0.031
30	4.7	0.071
31	9.5	1.2
32	0.50	0.089
33	2.8	0.18
34	4.0	3.4
35	5.6	0.25
36	0.25	0.21
37	2.4	0.25
38	4.0	0.42
39	1.2	0.09
40	0.50	0.31
41	0.84	0.21

TABLE 5

Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
42	1.7	0.089
43	13	1.1
44	13	0.50
45	2.0	0.50
46	0.71	0.50
47	4.7	0.57
48	4.8	0.50
49	0.71	0.083
50	0.12	0.054
51	0.84	0.22
52	0.59	0.11
53	0.35	0.25
54	1.7	0.56
55	13	1.7
56	19	1.0
57	0.35	0.041
58	5.7	0.76
59	51	0.42
60	19	3.0
61	16	0.65
62	9.5	0.22
63	54	0.66
64	0.71	0.077
65	2.4	0.20
66	16	0.76
67	1.7	0.16
68	6.7	0.25
69	13	0.44
70	2.0	0.092
71	11	0.57
72	4.7	0.28
73	11	0.25
74	11	0.33
75	16	0.50
76	8.0	0.29
78	16	0.76
79	0.84	0.042
80	1.7	0.25
81	1.0	0.042
82	22	0.50
83	54	1.7
84	23	0.66
85	3.4	0.11
86	1.4	0.036
87	0.71	0.047

TABLE 5

Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
88	1.7	0.055
89	11	0.44
90	0.71	0.041
91	2.8	0.11
92	1.7	0.082
93	0.42	0.042
94	0.50	0.041
95	1.7	0.054
96	1.4	0.11
97	0.71	0.054
98	2.4	0.095
99	72	0.76
100	0.71	0.042
101	4.0	0.25
102	2.0	0.13
103	4.0	0.33
104	1.2	0.062
105	0.84	0.062
106	0.71	0.034
107	0.59	0.082
108	0.84	0.04
109	72	0.22
110	1.7	0.047
111	0.71	0.031
112	1.4	0.072
113	0.84	0.054
114	0.59	0.031
115	8.0	0.19
116	0.42	0.031
117	4.8	0.14
118	0.84	0.048
119	0.59	0.048
120	1.0	0.072
121	1.0	0.063
122	1.0	0.054
123	1.0	0.041
124	0.84	0.047
125	3.4	0.14
126	2.4	0.11
127	1.2	0.33
128	2.0	0.11
129	27	1.52
130	4.8	0.22
131	0.84	0.028
132	1.2	0.048

TABLE 5

Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
133	4.0	0.13
134	2.0	0.13
135	4.8	0.22
136	23	0.76
137	6.7	0.38
138	38	0.87
139	23	0.38
140	6.7	0.19
141	8.0	0.25
142	45	1.5
143	2.0	0.048
144	11	9.2
145	64	1.3
146	64	1.5
147	25	1.3
148	0.15	0.052
149	45	0.66
150	1.7	0.25
151	4.5	0.14
152	27	1.2
153	1.4	0.083
154	2.8	0.072
155	128	1.3
156	5.7	0.17
157	2.0	0.054
158	1.7	1.0
159	27	0.50
160	9.5	0.22
161	23	0.44
162	4.8	0.12
163	2.0	0.87
164	1.7	0.11
165	4.0	0.062
166	1.7	0.055
167	1.0	0.055
168	3.4	0.10
169	19	0.50
170	8.0	0.22
171	9.5	0.22
172	3.4	0.13
173	2.0	0.12
174	19	0.76
175	9.5	0.22
176	1.2	0.13
178	2.8	0.13

TABLE 5

Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
179	1.7	0.060
180	>128	0.71
181	8.0	0.060
182	13	0.250
183	23	0.130
184	27	0.570
185	4.7	0.060
186	11	0.290
189	2.4	0.10
190	6.7	0.29
191	6.7	0.57
192	0.84	0.035
193	2	0.072
194	2.4	0.083
195	2.0	0.042
196	1.7	0.027
197	1.2	0.16
198	3.4	0.062
199	1.4	0.036
200	1.4	0.041
201	1.2	0.44
202	1.4	0.76
203	1.0	0.036
204	0.71	0.031
205	1	0.036
206	1.7	0.095
207	1.2	0.50
208	2.8	0.17
209	1.2	0.136
210	0.84	0.041
211	0.35	0.024
212	0.50	0.036
213	1.0	0.55
214	0.71	0.024
215	2.8	0.25
216	0.35	0.032
217	13	0.57
218	1.0	0.11
219	0.71	0.044
220	0.71	0.05
221	0.71	0.041
222	0.84	0.072
223	0.79	0.055
224	0.63	0.055
225	0.63	0.072

TABLE 5

Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
226	1.6	0.041
227	0.71	0.11
228	1.0	0.14
229	0.50	0.024
230	0.35	0.031
231	1.7	0.11
232	0.71	0.29
233	1.7	1.7
234	2	2
235	2.4	0.25
236	1.4	0.5
237	1.0	0.048
238	1.4	0.14
239	2.8	0.095
240	1.19	0.055
241	1.4	0.048

A number of the lactic acid bacteria including all Leuconostocs, all Pediococci, and some Lactobacilli, are intrinsically resistant to vancomycin. With the increased use of vancomycin, infections due to these bacteria have been reported with increasing frequency in immunocompromised patients (Handwerger et al., Reviews of Infectious Disease 12:602-610 (1990); Ruoff et al., Journal of Clinical Microbiology 26:2064-2068 (1988)). One important aspect of the antimicrobial activity of the formula I compounds is their activity against the vancomycin-resistant lactic acid bacteria. The compounds of the present are useful in inhibiting the growth of vancomycin-resistant lactic bacteria such as Leuconostoc, Pedicocci, and Lactobacilli and thus, controlling opportunistic infections by this group of bacteria. This activity is illustrated in Table 6, which summarizes a comparison of the activity of illustrative compounds against representative vancomycin-resistant lactic acid bacteria (*Pedicoccus acidilacti Pedicoccus pentosaceus, Leuconostoc lactis, Leuconostoc mesenteroides, Leuconostoc pseudomesenteroides, Leuconostoc citreum, and Lactobacillus confusus*, mean geometric MIC (mcg/mL)), as determined using a standard agar dilution assay on brain-heart infusion agar.

Table 6
In Vitro Activity of Formula I Compounds
MIC (mcg/ml)/Compound

	Pediococcus acidilacti (mean of 10)	Pediococcus pentosaceus (mean of 2)	Leuconostoc lactis (mean of 2)	Leuconostoc mesenteroides (mean of 4)	Leuconostoc pseudomesenteroides	Leuconostoc citreum	Lactobacillus confusus
Vancomycin	891	1024	1024	1024	>1024	>1024	1024
A82846B	141	>256	64	>256	>256	>256	>256
1	18	23	23	64	>128	>128	64
2	5.9	11	4.0	16	32	64	16
4	7.5	16	16	16	32	128	32
5	2.8	8.0	8.0	8	16	64	16
6	4.3	8.0	8.0	9.5	16	64	16
14	3.7	5.7	8.0	11	32	64	32
29	4.0	8.0	5.7	6.7	16	32	8
32	12.1	16	16	16	32	64	16
36	9.2	16	16	16	32	32	32
39	26	32	32	32	64	>64	32
41	71	91	91	91	>128	>128	64
49	55	64	64	64	128	128	64
50	51	64	64	64	128	128	64
51	87	91	64	76	>128	>128	64
52	55	64	64	76	64	>128	64
58	55	64	64	64	128	128	64
108	12	23	8.0	10	32	64	16
118	16	16	11	13	32	64	16
122	24	16	16	16	32	64	16
124	20	16	16	16	64	64	16

Pharmaceutical formulations of the formula I compounds are also part of this invention. Thus, the compound, preferably in the form of a pharmaceutically acceptable salt, can be formulated for oral or parenteral administration for the therapeutic or prophylactic treatment of bacterial infections.

For example, the compound can be admixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, wafers, and the like. The compositions comprising a formula I compound will contain from about 0.1 to about 90% by weight of the active compound, and

more generally from about 10 to about 30%. The compositions may contain common carriers and excipients, such as corn starch or gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride, and alginic acid.

Disintegrators commonly used in the formulations of this invention include croscarmellose, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose.

Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica.

Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used.

It may be desirable to add a coloring agent to make the dosage form more attractive in appearance or to help identify the product.

For intravenous (IV) use, a water soluble form of the antibiotic can be dissolved in one of the commonly used intravenous fluids and administered by infusion. Such fluids as, for example, physiological saline, Ringer's solution, or 5% dextrose solution can be used.

For intramuscular preparations, a sterile formulation of a suitable soluble salt form of the compound, for example the hydrochloride salt, can be dissolved and administered in a pharmaceutical diluent such as pyrogen-free water (distilled), physiological saline or 5% glucose solution. A suitable insoluble form of the compound may be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, for example, an ester of a long chain fatty acid such as ethyl oleate.

For oral use, a sterile formulation of a suitable salt form of the antibiotic, for example, the hydrochloride salt, formulated in a diluent such as distilled or deionized water, is particularly useful.

Alternatively, the unit dosage form of the antibiotic can be a solution of the antibiotic, preferably in its salt form, in a suitable diluent in sterile, hermetically sealed ampoules. The concentration of the antibiotic in the unit dosage may vary, for example, from about 1 percent to about 50 percent depending on the particular form of the antibiotic and its solubility and the dose desired by the physician.

In a further aspect, this invention provides a method for treating infectious diseases, especially those caused by Gram-positive microorganisms, in animals. The compounds of this invention are particularly useful in treating infections caused by methicillin-resistant staphylococci. Also, the compounds are useful in treating infection due to enterococci. Examples of such diseases are severe staphylococcal infections, for example, staphylococcal endocarditis and staphylococcal septicemia. The animal may be either susceptible to, or infected with, the microorganism. The method comprises administering to the animal an amount of a formula I compound which is effective for this purpose. In general, an effective amount of a formula I compound is a dose between about 0.5 and about 100 mg/kg. A preferred dose is from about 1 to about 60 mg/kg of active compound. A typical daily dose for an adult human is from about 50 mg to about 5 g.

In practicing this method, the antibiotic can be administered in a single daily dose or in multiple doses per day. The treatment regimen may require administration over extended periods of time, for example, for several days or for from one to six weeks. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the patient, the tolerance of the patient to the antibiotic and the microorganism or microorganisms involved in the infection.

A convenient method of practicing the treatment method is to administer the antibiotic via intravenous infusion. In this procedure a sterile formulation of a suitable soluble salt of the antibiotic is incorporated in a physiological fluid, such as 5% dextrose solution, and the resulting solution is infused slowly IV. Alternatively, the piggy-back method of IV infusion can also be used.

In order to illustrate more fully the operation of this invention, the following examples are provided, but are not to be construed as a limitation on the scope of the invention.

EXAMPLE 1

METHOD A

Preparation of Compound 2

A mixture of A82846B·triacetate, (2.25 g, 1.27 mmol, 1.0 equivalents (eq)) in 1:1 DMF/methanol (140 mL) under an atmosphere of argon was treated with 4-biphenylcarboxaldehyde (331 mg, 2.12 mmol, 1.7 eq). The resulting mixture was heated to 70°C and maintained as such for 1.75-2 hours. The solution was then treated with sodium cyanoborohydride (554 mg, 8.83 mmol, 6.9 eq). Heating at 70°C was continued for an additional 1.75-2 hours after which the reaction mixture was cooled to room temperature, concentrated *in vacuo*, diluted

with water (150 mL), and lyophilized to give a solid.

The solid was purified by preparative reverse-phase high performance liquid chromatography (HPLC) using a Waters 3 x (40 x 100 mm) C18 Nova-Pak cartridge with Waters C18 Nova-pak guard insert and utilizing TEAP buffer system. The analytical method for analysis was: 0.2% TEA/phosphoric acid (TEAP), pH = 3, the gradient system at time 0 was 5% CH_3CN/94.8% H_2O with 0.2% TEAP held constant and at 20 minutes was 60% CH_3ON/39.8% H_2O with 0.2% TEAP held constant. The UV wavelength used was 235 nm and the flow rate was 2 ml/minute. Analysis was done using a Waters Nova-pak C18 RCM column (8 X 100mm) with a Nova-pak C18 guard insert. It is necessary to desalt the product after reverse phase purification when this HPLC method is used.

Desalting was accomplished by adding the purified product to 5-10 ml of H_2O. 1 N HCl was added dropwise with stirring to dissolve the sample. The pH at this point was approximately 1-3. The pH of the solution was then raised to 8.2 with 1 N NaOH. A white solid precipitated out of solution. The mixture was cooled, filtered, and dried under vacuum at room temperature for 8-15 hours to give the zwitter ion (or neutral compound) of the desired product, compound 2 (*p*-phenylbenzyl·A82846B), (1.02 g, 45%).

EXAMPLE 2

Preparation of Compound 4

A mixture of A82846B.triacetate (1.5 g, 0.848 mmol, 1.0 eq) in methanol (100 mL) under an atmosphere of argon was treated with *p*-phenoxybenzaldehyde (298 mg, 1.51 mmol, 1.8 eq). The resulting mixture was heated to reflux and maintained as such for 2 hours. The solution was then treated with sodium cyanoborohydride (326 mg, 5.18 mmol, 6.1 eq). Heating at reflux was continued for an additional 2 hours after which the reaction mixture was cooled to room temperature and evaporated to dryness *in vacuo*.

The product was purified by reverse-phase HPLC with a TFA buffer. The analytical method for analysis was accomplished by using a Waters Nova-pak C18 RCM column (8 x 100 mm) with a Nova-pak C18 guard insert, eluting with a 2.0 ml/minute linear gradient of 15% acetonitrile/0.1% TFA at time zero to 80% acetonitrile/0.1% TFA at 15 minutes. The fractions containing the products were detected by ultraviolet scan at 235 nm. The organic solvent of the desired fractions was removed and the mixture was lyophilized to a white solid to give 0.618 mg of *p*-phenoxybenzyl·A82846B compound 4·tris(trifluroacetate) salt (20% yield). No desalting or further purification was necessary. This method is also especially useful in the preparation of Compound 2 wherein phenylbenzaldehyde is one of the starting materials.

EXAMPLE 3

Method B

Preparation of Compound 176

A mixture of A82846B.triacetate (280 mg, 0.157 mmol, 1.0 eq) in 1:1 DMF/methanol (30 mL) was treated with 8-phenyloctanal (59 mg, 0.29 mmol, 1.8 eq) and sodium cyanoborohydride (60 mg, 0.95 mmol, 6.1 eq). The resulting mixture was heated, under an atmosphere of nitrogen, to 70°C and maintained as such for 1 hour. The reaction mixture was then cooled to room temperature and concentrated in vacuo to give a residue. Purification of the product was accomplished by reverse-phase preparative HPLC utilizing a Waters 2 x (40 x 100 mm) C18 Nova-Pak cartridge with Waters C18 Nova-Pak guard insert. Elution was accomplished with a 30 minute linear gradient (time=0 minutes 95% TEAP (0.5% aqueous triethylamine adjusted to pH=3 with phosphoric acid)/5% CH_3CN to t = 30 minutes 20% TEAP/80% CH_3CN) with a flow rate of 40 mL/minute and UV detection at 280 nm. The desired fraction was concentrated in vacuo then desalted with a Waters Sep-Pak cartridge as described below. This afforded compound 176 in 22% yield (60 mg).

The resulting compound was desalted as follows. A Waters Sep-Pak cartridge was pre-wet with methanol (2-3 column volumes) then conditioned with water (2-3 column volumes). The sample, dissolved in a minimum volume of water, was loaded onto the Sep-Pak column which was then washed with water (2-3 column volumes) to remove the unwanted salts. The product was then eluted with an appropriate solvent system, typically 1:1 CH_3CN/H_2O, CH_3CN, and/or methanol. The organic solvent component was removed *in vacuo* and the resulting aqueous solution lyophilized to give the final product.

EXAMPLE 4

Preparation of Compound 229

A three liter 3-necked flask was fitted with a condenser, nitrogen inlet and overhead mechanical stirring apparatus. The flask was charged with pulverized A82846B acetate salt (20.0 g, 1.21×10^{-3} mol) and methanol (1000 mL) under a nitrogen atmosphere. 4'-chlorobiphenylcarboxaldehyde (2.88 g, 1.33×10^{-2} mol, 1.1 eq.) was added to this stirred mixture, followed by methanol (500 mL). Finally, sodium cyanoborohydride (0.84 g, 1.33×10^{-2} mol, 1.1 eq.) was added followed by methanol (500 mL). The resulting mixture was heated to reflux (about 65°C).

After 1 hour at reflux, the reaction mixture attained homogeneity. After 25 hours at reflux, the heat source was removed and the clear reaction mixture was measured with a pH meter (6.97 at 58.0°C). 1 N NaOH (22.8 mL) was added dropwise to adjust the pH to 9.0 (at 54.7°C). The flask was equipped with a distillation head and the mixture was concentrated under partial vacuum to a weight of 322.3 grams while maintaining the pot temperature between 40-45°C.

The distillation head was replaced with an addition funnel containing 500 mL of isopropanol (IPA). The IPA was added dropwise to the room temperature solution over 1 hour. After approximately 1/3 of the IPA was added, a granular precipitate formed. The remaining IPA was added at a faster rate after precipitation had commenced. The flask was weighed and found to hold 714.4 grams of the IPA/methanol slurry.

The flask was re-equipped with a still-head and distilled under partial vacuum to remove the remaining methanol. The resulting slurry (377.8 g) was allowed to chill in the freezer overnight. The crude product was filtered through a polypropylene pad and rinsed twice with 25 mL of cold IPA. After pulling dry on the funnel for 5 minutes, the material was placed in the vacuum oven to dry at 40°C. A light pink solid (22.87 g (theory = 22.43 g)) was recovered. HPLC analysis versus a standard indicated 68.0% weight percent of Compound 229 (4-[4-chlorophenyl]benzyl-A82846B] in the crude solid, which translated into a corrected crude yield of 69.3%.

The products of the reaction were analyzed by reverse-phase HPLC utilizing a Zorbax SB-C18 column with ultraviolet light (UV; 230 nm) detection. A 20 minute gradient solvent system consisting of 95% aqueous buffer/5% CH_3CN at time=0 minutes to 40% aqueous buffer/60% CH_3CN at time=20 minutes was used, where the aqueous buffer was TEAP (5 ml CH_3CN, 3 ml phosphoric acid in 1000 ml water).

EXAMPLE 5

Table 7 summarizes the preparation and certain physical characteristics of the exemplified compounds. The yield of the product was calculated using the amount of the formula II compound as the limiting reagent. The following terms are found in Table 6 and are defined here. "Method" refers to the method of synthesis as described in Examples 1 and 2, or 3. "Reagent Equivalents" refers to the molar equivalents of the aldehyde and reducing agent relative to the formula II compound. "FAB-MS (M+3H)" refers to Fast atom bombardment-mass spectrometry.

TABLE 7

Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
1	28	A/1:1	1.7/6.9	1733*
2	45	A/1:1	1.7/6.9	1760
3	28	A/1:1	1.8/7.6	1732**
4	20	A/0:1	1.8/6.1	1776***
5	30	A/0:1	1.8/6.1	1790
6	10	A/0:1	1.8/6.1	1768***
7	55	A/0:1	1.8/6.1	1740***
8	16	A/0:1	1.8/6.1	1826
9	32	A/0:1	1.8/6.1	1764***
10	6	A/0:1	1.8/6.1	1868
11	38	A/0:1	1.8/6.1	1784
12	46	A/0:1	1.8/6.1	1940
13	32	A/0:1	1.8/6.1	1783**
14	5.4	A/1:1	1.9/4.2	1859
15	42	A/0:1	1.8/6.1	1763
16	39	A/0:1	1.8/6.1	1807**
17	41	A/0:1	1.8/6.1	1798
18	27	A/0:1	1.8/6.1	1817
19	30	A/0:1	1.8/6.1	1739
20	5	A/1:1	1.8/1.8	1775*
21	11	A/1:1	1.8/1.8	1872*
22	8	A/1:1	1.8/1.8	1829**
23	ND	A/0:1	1.8/3.6	1888***
24	34	A/0:1	1.7/2.5	1685
25	31	A/0:1	1.8/1.6	1779
26	30	A/0:1	1.7/2.5	1685
27	19	A/0:1	1.8/2.5	1734**
28	35	A/0:1	1.6/1.6	1735
29	39	A/0:1	1.6/1.6	1785**
30	29	A/0:1	1.6/1.6	1734**
31	11	A/0:1	1.7/2.5	1684**
32	28	A/0:1	1.5/1.6	1771**
33	ND	A/1:1	1.8/1.8	1789
34	ND	A/1:1	1.8/1.8	1836
35	ND	A/1:1	1.8/1.8	1785
36	ND	A/1:1	1.8/1.8	1835
37	31	A/0:1	1.5/1.5	1752***
38	16	A/0:1	1.5/1.6	1709
39	46	A/0:1	1.5/1.5	1773
40	29	A/1:1	1.8/1.8	1846*
41	46	A/0:1	1.5/1.5	1729
42	53	A/0:1	1.5/1.5	1780
43	22	A/0:1	1.1/1.5	1799***
44	42	A/0:1	1.5/1.5	1749

TABLE 7

Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
45	50	A/0:1	1.1/1.5	1841
46	38	A/0:1	1.1/1.5	1850
47	40	A/0:1	1.5/1.5	1687
48	22	A/0:1	1.5/1.5	1728***
49	44	A/0:1	1.5/1.5	1776***
50	32	A/1:10	2.0/1.5	1774
51	32	A/0:1	1.5/1.5	1820
52	31	A/0:1	1.5/1.5	1819**
53	43	A/0:1	1.5/1.5	1896
54	4	A/1:1	1.8/1.8	1789
55	21	A/0:1	1.5/1.5	1767
56	20	A/0:1	1.1/1.5	1741
57	29	A/0:1	1.5/1.5	1820**
58	22	A/0:1	1.5/1.5	1727
59	ND	A/1:1	1.8/1.8	1803
60	33	A/0:1	1.1/1.5	1777**
61	24	A/0:1	1.1/1.5	1723
62	ND	A/1:1	1.8/1.8	1789**
63	ND	A/1:1	1.8/1.8	1789**
64	30	A/0:1	1.5/1.5	1805
65	24	A/0:1	1.1/1.5	1763
66	17	A/0:1	1.1/1.5	1704***
67	22	A/0:1	1.1/1.5	1766***
68	ND	A/1:1	1.8/1.8	1802
69	ND	A/1:1	1.8/1.8	1803
70	44	A/0:1	1.1/1.5	1821
71	4	A/0:1	1.1/1.5	1796***
72	32	A/0:1	1.5/1.5	1750***
73	ND	A/1:1	1.8/1.8	1753
74	17	A/0:1	1.1/1.5	1815
75	23	A/0:1	1.5/1.5	1806***
76	16	A/1:1	1.8/1.8	1711
77	ND	A/1:1	1.8/1.8	1742
78	5	A/1:1	1.8/1.8	1728
79	ND	A/1:1	1.8/1.8	1783**
80	46	A/0:1	1.5/1.5	1843****
81	52	A/0:1	1.5/1.5	1844***
82	29	A/0:1	1.5/1.5	1726***
83	7	A/0:1	1.5/1.5	1798**
84	8	A/0:1	1.5/1.5	1700
85	30	A/0:1	1.5/1.5	1775
86	45	A/0:1	1.5/1.5	1809
87	42	A/0:1	1.1/1.5	1854**
88	36	A/0:1	1.1/1.5	1854**

TABLE 7

Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
89	43	A/1:1	1.8/1.8	1711
90	13	A/1:1	1.8/1.8	1787
91	20	A/1:10	1.5/1.5	1759**
92	23	A/1:10	1.5/1.5	1777
93	42	A/0:1	1.5/1.5	1823
94	41	A/0:1	1.1/1.5	1854**
95	49	A/0:1	1.1/1.5	1789**
96	34	A/0:1	1.1/1.5	1832
97	42	A/1:10	1.5/1.5	1773**
98	31	A/0:1	1/1.5	1805
99	ND	A/1:1	1.8/1.8	1770**
100	ND	A/1:1	1.8/1.8	1787
101	34	A/1:1	1.19/1.8	1761
102	41	A/0:1	1.5/1.5	1805
103	37	A/0:1	1/1.5	1788***
104	34	A/0:1	1.1/1.5	1819**
105	ND	A/1:1	1.7/2.0	1838*
106	ND	A/1:1	1.7/2.0	1844
107	ND	A/1:1	1.1/1.1	1802
108	ND	A/0:1	1.8/1.8	1791**
109	ND	A/0:1	1.8/1.8	1789
110	15	A/0:1	1.1/1.5	1881
111	ND	A/1:1	1.8/1.8	1843
112	16	A/1:1	1.8/1.8	1764
113	45	A/0:1	1.1/1.5	1805**
114	52	A/0:1	1.1/1.5	1888**
115	39	A/0:1	1.1/1.5	1791
116	ND	A/1:1	1.8/2.0	1834
117	29	A/0:1	1.5/1.7	1803**
118	28	A/0:1	2/1.5	1765**
119	41	A/0:1	1/1.5	1843
120	38	A/0:1	1.1/1.5	1757
121	41	A/0:1	1.1/1.5	1799
122	24	A/1:1	1.8/2.6	1863
123	55	A/0:1	1.1/1.5	1795**
124	17	A/1:10	3/1.5	1781**
125	36	A/0:1	1.5/1.8	1841
126	26	A/0:1	1.6/1.8	1818
127	54	A/0:1	1.1/1.5	1810
128	34	A/0:1	1.4/1.8	1831
129	ND	A/1:1	1.4/1.8	1780
130	4	A/0:1	1.1/1.5	1795**
131	42	A/0:1	1.1/1.5	1834**

TABLE 7

Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
132	49	A/0:1	1.1/1.5	1843
133	41	A/0:1	1.1/1.5	1855
134	30	A/0:1	1.1/1.5	1801**
135	ND	A/1:1	1.8/1.8	1779
136	ND	A/1:1	1.8/1.8	1699
137	ND	A/1:1	1.8/1.8	1760
138	ND	A/1:1	1.8/1.8	1741
139	13	A/1:10	2.4/1.5	1749**
140	11	A/1:10	2.9/1.5	1750*
141	ND	A/1:1	2.3/5.3	1742
142	ND	A/1:1	2.5/5.4	1826
143	ND	A/1:1	1.8/1.8	1861
144	ND	A/1:1	1.5/1.5	1922
145	ND	A/1:1	1.1/1.1	1716
146	ND	A/1:1	1.35/1.8	1780*
147	ND	A/1:1	1.5/1.8	1769
148	31	A/1:10	3/1.5	1857
149	18	A/0:1	1.1/1.5	1777
150	22	A/1:1	2/4.8	1803
151	ND	A/1:1	1.8/1.8	1760
152	ND	A/1:1	1.8/1.8	1826****
153	22	A/1:10	2.5/1.6	1782
154	ND	A/1:1	1.8/1.8	1780
155	13	A/0:1	1.6/1.6	1768
156	41	A/1:9	1.2/1.6	1788
157	9	A/1:1	2.7/5.4	1810
158	ND	A/1:1	1.8/4.1	1854
159	13	A/1:9	1/1.6	1807
160	13	A/1:9	0.95/1.6	1774
161	ND	A/1:1	1.8/1.8	1690
162	ND	A/1:1	3.1/6.9	1804
163	ND	A/1:1	1.9/5.3	1854
164	ND	A/1:1	1.8/1.8	1772
165	21	A/1:1	2.0/4.9	1810
166	20	A/1:1	2.0/6.2	1870
167	23	A/1:1	1.8/4.1	1914
168	ND	A/1:1	1.8/1.8	1737
169	15	A/1:1	1.8/4.1	1700
170	39	A/0:1	1.2/1.1	1728
171	32	A/0:1	1.2/1.5	1729**
172	11	B/1:1	2.2/4.8	1755**
173	51	A/1:9	1.3/1.7	1909
174	35	A/1:9	1.5/1.6	1816

TABLE 7

Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
175	22	B/1:1	1.9/6.2	1742
176	21	B/1:1	1.8/6.1	1782
177	ND	A/1:1	3.6/1.8	1774
178	33	A/1:9	1.4/1.7	1788**
179	22	B/1:1	1.8/3.8	1748
180	16	A/1:1	1.1/1.3	1591***
181	14	A/1:1	1.1/1.3	1617
182	17	A/0:1	1.6/6.3	1725
183	17	A/0:1	1.6/6.3	1691**
184	8	A/0:1	1.6/6.26	1707**
185	21	A/1:1	1.1/3.0	1725**
186	8	A/1:1	1.1/3.0	1630**
187	16	A/1.1	1.6/3.0	2110**
188	6	A/1.1	1.5/5.0	2976**
189	20	A/1:10	1/1.2	1747**
190	9	A/1:10	1.5/1.5	1716
191	18	B/1:1	1.8/4.1	1771**
192	11	A/0:1	ND/1.8	1738
193	24	A/1:10	2.0/1.5	1820**
194	27	A/1:10	2.0/1.5	1821
195	18	B/1:1	1.6/3.6	1798
196	18	B/1:1	1.8/3.9	1754
197	35	B/1:1	1.5/3.5	1810
198	14	B/1:1	1.5/3.7	1784
199	ND	B/1:1	1.5/2.8	1772
200	11	B/1:1	1.5/3.7	1828
201	14	B/1:1	1.8/6.3	1873**
202	7	B/1:1	1.3/5.9	1889**
203	15	A/0:1	1.1/1.1	1843
204	16	B/1:1	2.0/5.6	1746
205	23	B/1:1	1.8/3.7	1732
206	11	A/0:1	1.1/1.1	1777
207	11	B/1:1	1.6/4.2	1813**
208	26	B/1:1	1.9/3.9	1703
209	20	A/1:1	1.0/1.6	1774
210	35	A/0:1	1.0/1.0	1788
211	26	A/0:1	1.3/1.8	1777
212	48	A/1:1	1.1/3.1	1849**
213	56	A/1:1	1.0/3.6	1849**
214	9	B/1:1	1.9/1.9	1732
215	35	A/0:1	1.3/1.8	1820***
216	31	A/0:1	1.3/1.8	1828***
217	12	B/1:1	2.0/2.1	1676
218	24	A/1:10	1.2/1.5	1766***

TABLE 7

Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
219	24	A/1:1	1.4/3.5	1860
220	21	A/0:1	1.3/1.8	1785
221	42	A/0:1	1.3/1.8	1787
222	20	A/0:1	1.1/1.1	1787
223	32	A/1:1	2.4/4.5	1817**
224	36	A/1:1	1.6/5.6	1773**
225	ND	A/0:1	1.1/1.1	1787
226	28	A/1:1	1.5/3.0	1766*
227	22	A/1:1	1.2/3.7	1777**
228	21	A/0:1	1/1.1	1848**
229	16	A/0:1	1/1.2	1793
230	27	A/0:1	1.3/1.8	1838***
231	36	A/0:1	1.3/1.8	1785*
232	32	A/1:1	1.8/4.6	1806
233	5	A/1:1	1.1/7.3	1878
234	7	B/1:1	1.5/3.5	1836*
235	15	B/1:1	1.4/4.8	1750
236	4	B/1:1	1.4/6.3	1819**
237	14	A/0:1	1.1/1.1	1787
238	25	B/0:1	1.1/1.1	1771
239	22	B/1:1	1.6/1.5	1810
240	4.7	A/1:60	1.2/1.1	1810***
241	24	B/1:1	1.1/2.5	1779**
242	N.D.	A/1:50	1.1/1.2	1787
243	20	A/0:1	1.1/1.1	1790
244	24	C/0:1	1.1/1.1	1808
N.D.= Not determined				
*M+H				
**M+2H				
***M+4H				
****M+6H				

EXAMPLE 6

Capsule Formulation

Capsules containing 250 mg of Compound 2 are prepared using the following ingredients:

Ingredient	Weight
Compound 2 HCl salt	255.4 mg
Corn starch flowable powder	150 mg
Corn starch	144.6 mg

Compound 2 (HCl salt form, 255.4 mg), corn starch flowable powder (150 mg) and corn starch (144.6 mg) are

blended in a suitable mixer until homogenous. The mixture is used to fill a hard gelatin capsule to a net fill weight of 550 mg.

EXAMPLE 7

Capsule Formulation

Capsules containing 250 mg of Compound 229 are prepared using the following ingredients:

Ingredient	Weight
Compound 229 HCl salt	255.4 mg
Corn starch flowable powder	150 mg
Corn starch	144.6 mg

Compound 2 (HCl salt form, 255.4 mg), corn starch flowable powder (150 mg) and corn starch (144.6 mg) are blended in a suitable mixer until homogenous. The mixture is used to fill a hard gelatin capsule to a net fill weight of 550 mg.

EXAMPLE 8

Suspension Formulation

A sterile insoluble form of compound 2 is milled or screened to a particle size suitable for suspension. This particulate material is suspended in the following vehicle:

Ingredient	Weight
Lecithin	1%
Sodium citrate	2%
Propylparaben	0.015%
Distilled water	q.s. to desired volume

EXAMPLE 9

Suspension Formulation

A sterile insoluble form of compound 229 is milled or screened to a particle size suitable for suspension. This particulate material is suspended in the following vehicle:

Ingredient	Weight
Lecithin	1%
Sodium citrate	2%
Propylparaben	0.015%
Distilled water	q.s. to desired volume

EXAMPLE 10

Tablet Formulation

Tablets containing 250 mg of compound 2 are prepared with the following composition:

Ingredient	Weight
Lecithin	1%
Sodium citrate	2%
Propylparaben	0.015%
Distilled water	q.s. to desired volume

EXAMPLE 11

Tablet Formulation

Tablets containing 250 mg of compound 229 are prepared with the following composition:

Ingredient	Weight
Lecithin	1%
Sodium citrate	2%
Propylparaben	0.015%
Distilled water	q.s. to desired volume

EXAMPLE 12

Tablet Formulation

Tablets containing 250 mg of compound 2 are prepared with the following composition:

Ingredient	Weight
Compound 2 HCl salt	255.4 mg
Microcrystalline cellulose	101.1 mg
Croscarmellose sodium	12.0 mg
Providone	12.0 mg
Magnesium stearate	3.0 mg
Stearic acid	4.0 mg
Purified water	0.16 ml

EXAMPLE 13

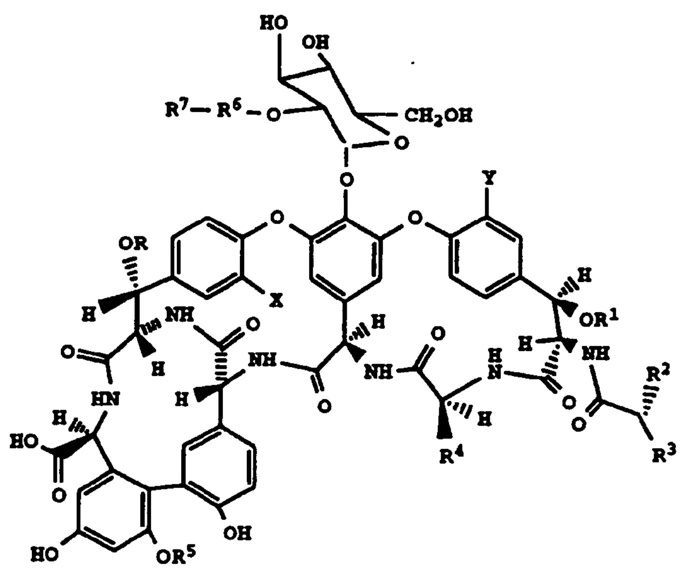
Tablet Formulation

Tablets containing 250 mg of compound 229 are prepared with the following composition:

Ingredient	Weight
Compound 229 HCl salt	255.4 mg
Microcrystalline cellulose	101.1 mg
Croscarmellose sodium	12.0 mg
Providone	12.0 mg
Magnesium stearate	3.0 mg
Stearic acid	4.0 mg
Purified water	0.16 ml

Claims

1. A compound of the formula:



or salt thereof, wherein:

X and Y are each independently hydrogen or chloro;

R is hydrogen, 4-*epi*-vancosaminyl, actinosaminyl, or ristosaminyl;

R^1 is hydrogen, or mannose;

R^2 is $-NH_2$, $-NHCH_3$, or-$N(CH_3)_2$;

R^3 is $-CH_2CH(CH_3)_2$, [*p*-OH, *m*-Cl]phenyl, *p*-rhamnose-phenyl, [*p*-rhamnose-galactose]phenyl, [*p*-galactose-galactose]phenyl, or [*p*-CH_3O-rhamnose]phenyl;

R^4 is $-CH_2(CO)NH_2$, benzyl, [*p*-OH]phenyl, or [*p*-OH, m-Cl]phenyl;

R^5 is hydrogen, or mannose;

R^6 is 4-*epi*-vancosaminyl, L-acosaminyl, L-ristosaminyl, or L-actinosaminyl;

R^7 is $(C_2$-$C_{16})$alkenyl, $(C_2$-$C_{12})$alkynyl, $(C_1$-C_{12} alkyl)-R_8, $(C_1$-C_{12} alkyl)-halo, $(C_2$-C_6 alkenyl)-R_8, $(C_2$-C_6 alkynyl)-R_8, $(C_1$-C_{12} alkyl)-O-R_8, and is attached to the amino group of R^6;

R^8 is selected from the group consisting of:

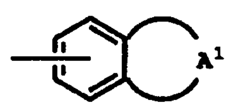
a) multicyclic aryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

(i) hydroxy,

(ii) halo,
(iii) nitro,
(iv) (C_1-C_6)alkyl,
(v) (C_1-C_6)alkenyl,
(vi) (C_1-C_6)alkynyl,
(vii) (C_1-C_6)alkoxy,
(viii) halo-(C_1-C_6)alkyl,
(ix) halo-(C_1-C_6)alkoxy,
(x) carbo-(C_1-C_6)alkoxy,
(xi) carbobenzyloxy,
(xii) carbobenzyloxy substituted with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, or nitro,
(xiii) a group of the formula $-S(O)_{n'}-R^9$, wherein n' is 0-2 and R^9 is (C_1-C_6)alkyl, phenyl, or phenyl substituted with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, or nitro, and
(xiv) a group of the formula $-C(O)N(R^{10})_2$ wherein each R^{10} substituent is independently hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, phenyl, or phenyl substituted with (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, halo, or nitro;

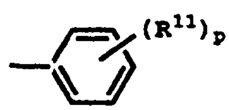
b) heteroaryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:
(i) halo,
(ii) (C_1-C_6)alkyl,
(iii) (C_1-C_6)alkoxy,
(iv) halo-(C_1-C_6)alkyl,
(v) halo-(C_1-C_6)alkoxy,
(vi) phenyl,
(vii) thiophenyl,
(viii) phenyl substituted with halo, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_1-C_6)alkoxy, or nitro,
(ix) carbo-(C_1-C_6)alkoxy,
(x) carbobenzyloxy,
(xi) carbobenzyloxy substituted with (C_1-C_6)alkyl, (C_1-C_6) alkoxyl, halo, or nitro,
(xii) a group of the formula $-S(O)_{n'}-R^9$, as defined above,
(xiii) a group of the formula $-C(O)N(R^{10})_2$ as defined above, and
(xiv) thienyl;

c) a group of the formula:



wherein A^1 is $-OC(A^2)_2-C(A^2)_2-O-$, $-O-C(A^2)_2-O-$,$-C(A^2)_2-O-$, or $-C(A^2)_2-C(A^2)_2-C(A^2)_2-C(A^2)_2-$, and each A^2 substituent is independently selected from hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)alkoxy, and (C_4-C_{10})cycloalkyl;

d) a group of the formula:

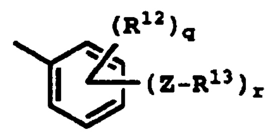


wherein p is from 1 to 5; and
R^{11} is independently selected from the group consisting of:
(i) hydrogen,
(ii) nitro,
(iii) hydroxy,
(iv) halo,
(v) (C_1-C_8)alkyl,

(vi) (C_1-C_8)alkoxy,
(vii) (C_9-C_{12})alkyl,
(viii) (C_2-C_9)alkynyl,
(ix) (C_9-C_{12})alkoxy,
(x) (C_1-C_3)alkoxy substituted with (C_1-C_3)alkoxy, hydroxy, halo(C_1-C_3)alkoxy, or (C_1-C_4)alkylthio,
(xi) (C_2-C_5)alkenyloxy,
(xii) (C_1-C_{13})alkynyloxy
(xiii) halo-(C_1-C_6)alkyl,
(xiv) halo-(C_1-C_6)alkoxy,
(xv) (C_2-C_8)alkylthio,
(xvi) (C_2-C_{10})alkanoyloxy,
(xvii) carboxy-(C_2-C_4)alkenyl,
(xviii) (C_1-C_3)alkylsulfonyloxy,
(xix) carboxy-(C_1-C_3)alkyl,
(xx) N-[di(C_1-C_3)-alkyl]amino-(C_1-C_3)alkoxy,
(xxi) cyano-(C_1-C_6)alkoxy, and
(xxii) diphenyl-(C_1-C_6)alkyl,

with the proviso that when R^{11} is (C_1-C_8)alkyl, (C_1-C_8)alkoxy, or halo, p must be greater or equal to 2, or when R^7 is $(C_1-C_3$ alkyl)-R^8 then R^{11} is not hydrogen, (C_1-C_8)alkyl, (C_1-C_8)alkoxy, or halo;

e) a group of the formula:



wherein q is 0 to 4;

R^{12} is independently selected from the group consisting of:
(i) halo,
(ii) nitro,
(iii) (C_1-C_6)alkyl,
(iv) (C_1-C_6)alkoxy,
(v) halo-(C_1-C_6)alkyl,
(vi) halo-(C_1-C_6)alkoxy, and
(vii) hydroxy, and
(vii) (C_1-C_6)thioalkyl;

r is 1 to 5; provided that the sum of q and r is no greater than 5;

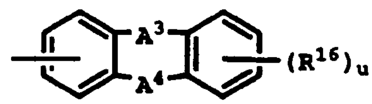
Z is selected from the group consisting of:
(i) a single bond,
(ii) divalent (C_1-C_6)alkyl unsubstituted or substituted with hydroxy, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy,
(iii) divalent (C_2-C_6)alkenyl,
(iv) divalent (C_2-C_6)alkynyl, or
(v) a group of the formula $-(C(R^{14})_2)s-R^{15}-$ or $-R^{15}-(C(R^{14})_2)_s-$, wherein s is 0-6; wherein each R^{14} substituent is independently selected from hydrogen, (C_1-C_6)-alkyl, or (C_4-C_{10}) cycloalkyl; and R^{15} is selected from -O-, -S-, -SO-, $-SO_2-$, $-SO_2-O-$, -C(O)-, -OC(O)-, -C(O)O-, -NH-, $-N(C_1-C_6$ alkyl)-, and -C(O)NH-, -NHC(O)-, N=N;

R^{13} is independently selected from the group consisting of:
(i) (C_4-C_{10})heterocyclyl,
(ii) heteroaryl,
(iii) (C_4-C_{10})cycloalkyl unsubstituted or substituted with (C_1-C_6)alkyl, or
(iv) phenyl unsubstituted or substituted with 1 to 5 substituents independently selected from: halo, hydroxy, nitro, (C_1-C_{10}) alkyl, (C_1-C_{10})alkoxy, halo-(C_1-C_3)alkoxy, halo-(C_1-C_3)alkyl, (C_1-C_3)alkoxyphenyl, phenyl, phenyl-(C_1-C_3)alkyl, (C_1-C_6)alkoxyphenyl, phenyl-(C_1-C_3)alkynyl, and (C_1-C_6)alkylphenyl;

f) (C_4-C_{10})cycloalkyl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:
(i) (C_1-C_6)alkyl,

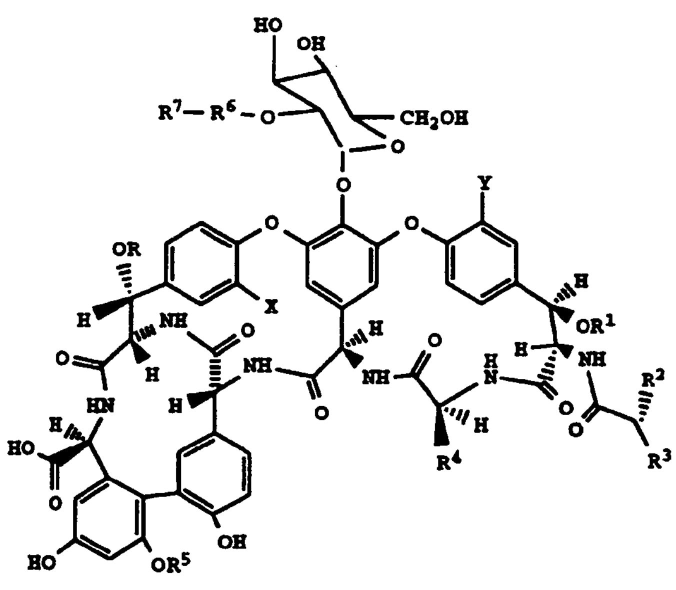
(ii) $(C_1\text{-}C_6)$alkoxy,
(iii) $(C_1\text{-}C_6)$alkenyl,
(iv) $(C_1\text{-}C_6)$alkynyl,
(v) $(C_4\text{-}C_{10})$cycloalkyl,
(vi) phenyl,
(vii) phenylthio,
(viii) phenyl substituted by nitro, halo, $(C_1\text{-}C_6)$alkanoyloxy, or carbocycloalkoxy, and
(ix) a group represented by the formula -Z-R^{13} wherein Z and R^{13} are as defined above; and

g) a group of the formula:



wherein
A^3 and A^4 are each independently selected from
(i) a bond,
(ii) -O-,
(iii) -$S(O)_t$-, wherein t is 0 to 2,
(iv) -$C(R^{17})_2$-, wherein each R^{17} substituent is independently selected from hydrogen, $(C_1\text{-}C_6)$alkyl, hydroxy, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, or both R^{17} substituents taken together are O,
(v) -$N(R^{18})_2$-, wherein each R^{18} substituent is independently selected from hydrogen; $(C_1\text{-}C_6)$alkyl; $(C_1\text{-}C_6)$alkenyl; $(C_1\text{-}C_6)$alkynyl; $(C_4\text{-}C_{10})$cycloalkyl; phenyl; phenyl substituted by nitro, halo, $(C_1\text{-}C_6)$alkanoyloxy; or both R^{18} substituents taken together are $(C_4\text{-}C_{10})$cycloalkyl;
R^{16} is R^{12} or R^{13} as defined above; and
u is 0-4.

2. A compound of the formula:



or salt thereof, wherein:
X and Y are each independently hydrogen or chloro;
R is hydrogen, 4-epi-vancosaminyl, actinosaminyl, or ristosaminyl;
R^1 is hydrogen, or mannose;
R^2 is $-NH_2$, $-NHCH_3$, or-$N(CH_3)_2$;
R^3 is $-CH_2CH(CH_3)_2$, phenyl, [p-OH,m-Cl]phenyl, p-rhamnose-phenyl, or [p-rhamnose-galactose]phenyl;

R^4 is $-CH_2(CO)NH_2$, benzyl, [*p*-OH]phenyl, or [*p*-OH, m-Cl]phenyl;
R^5 is hydrogen, or mannose;
R^6 is 4-*epi*-vancosaminyl, L-acosaminyl, L-ristosaminyl, or L-actinosaminyl;
R^7 is $-(CH_2)_n-R^8$, or $-C(CH_3)CH-R^8$, and is attached to the amino group of R^6;
n is 1-10;
R^8 is selected from the group consisting of:

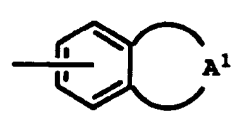
a) multicyclic aryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

(i) hydroxy,
(ii) halo,
(iii) nitro,
(iv) (C_1-C_6)alkyl,
(v) (C_1-C_6)alkenyl,
(vi) (C_1-C_6)alkynyl,
(vii) (C_1-C_6)alkoxy,
(viii) halo-(C_1-C_6)alkyl,
(ix) halo-(C_1-C_6)alkoxy,
(x) carbo-(C_1-C_6)alkoxy,
(xi) carbobenzyloxy,
(xii) carbobenzyloxy substituted with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, or nitro,
(xiii) a group of the formula $-S(O)_{n'}-R^9$, wherein n' is 0-2 and R^9 is (C_1-C_6)alkyl, phenyl, or phenyl substituted with (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo, or nitro, and
(xiv) a group of the formula $-C(O)N(R^{10})_2$ wherein each R^{10} substituent is independently hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, phenyl, or phenyl substituted with (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, halo, or nitro;

b) heteroaryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

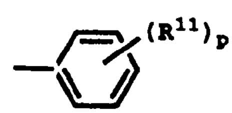
(i) halo,
(ii) (C_1-C_6)alkyl,
(iii) (C_1-C_6)alkoxy,
(iv) halo-(C_1-C_6)alkyl,
(v) halo-(C_1-C_6)alkoxy,
(vi) phenyl,
(vii) thiophenyl,
(viii) phenyl substituted with halo, (C_1-C_6)alkyl, (C_1-C_6)alkenyl, (C_1-C_6)alkynyl, (C_1-C_6)alkoxy, or nitro,
(ix) carbo-(C_1-C_6)alkoxy,
(x) carbobenzyloxy,
(xi) carbobenzyloxy substituted with (C_1-C_6)alkyl, (C_1-C_6) alkoxy, halo, or nitro,
(xii) a group of the formula $-S(O)_{n'}-R^9$, as defined above, and
(xiii) a group of the formula $-C(O)N(R^{10})_2$ as defined above;

c) a group of the formula:



wherein A^1 is $-OC(A^2)_2-C(A^2)_2-O-$, $-O-C(A^2)_2-O-$, $-C(A^2)_2-O-$, or $-C(A^2)_2-C(A^2)_2-C(A^2)_2-C(A^2)_2-$, and each A^2 substituent is independently selected from hydrogen, (C_1-C_6)-alkyl, (C_1-C_6)alkoxy, and (C_4-C_{10})cycloalkyl;

d) a group of the formula:

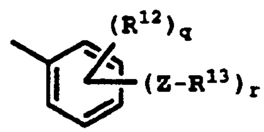


wherein p is from 1 to 5; and

R^{11} is independently selected from the group consisting of:

(i) nitro,
(ii) hydroxy,
(iii) (C_9-C_{12})alkyl,
(iv) (C_9-C_{12})alkoxy,
(v) (C_2-C_6)alkenyloxy,
(vi) halo-(C_1-C_6)alkyl,
(vii) halo-(C_1-C_6)alkoxy,
(viii) (C_2-C_6)alkylthio,
(ix) (C_1-C_6)alkynyl,
(x) (C_2-C_{10})alkanoyloxy,
(xi) carboxy-(C_2-C_4)alkenyl,
(xii) (C_1-C_3)alkylsulfonyloxy,
(xiii) carboxy-(C_1-C_3)alkyl,
(xiv) (C_1-C_3)alkoxy substituted with (C_1-C_3)alkoxy, hydroxy, halo(C_1-C_3)alkoxy, or (C_1-C_4)alkylthio,
(xv) N-[di(C_1-C_3)-alkyl]amino-(C_1-C_3)alkoxy,
(xvi) cyano-(C_1-C_6)alkoxy,
(xvii) (C_1-C_{12})alkyl, (C_1-C_{12})alkoxy, or halo when p is greater or equal to 2,
(xviii) diphenyl-(C_1-C_6)alkyl, and
(xix) hydrogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy when n greater or equal to 4;

e) a group of the formula:



wherein q is 0 to 4;

R^{12} is independently selected from the group consisting of:

(i) halo,
(ii) nitro,
(iii) (C_1-C_6)alkyl,
(iv) (C_1-C_6)alkoxy,
(v) halo-(C_1-C_6)alkyl,
(vi) halo-(C_1-C_6)alkoxy, and
(vii) hydroxy, and
(vii) (C_1-C_6)thioalkyl;

r is 1 to 5; provided that the sum of q and r is no greater than 5;

Z is selected from the group consisting of:

(i) a single bond,
(ii) divalent (C_1-C_6)alkyl unsubstituted or substituted with hydroxy, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy,
(iii) divalent (C_2-C_6)alkenyl,
(iv) divalent (C_2-C_6)alkynyl, or
(v) a group of the formula -$(C(R^{14})_2)_s$-R^{15}- or -R^{15}-$(C(R^{14})_2)_s$-, wherein s is 0-6; each R^{14} substituent is independently selected from hydrogen, (C_1-C_6)-alkyl, or (C_4-C_{10}) cycloalkyl; and R^{15} is selected from -O-, -S-, -SO-, -SO_2-, -SO_2-O-, -C(O)-, -OC(O)-, -C(O)O-, -NH-, -N(C_1-C_6 alkyl)-, and -C(O)NH-;

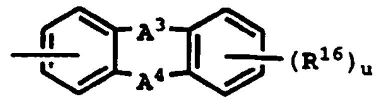
R^{13} is independently selected from the group consisting of:

(i) (C_4-C_{10})heterocyclyl,
(ii) heteroaryl,
(iii) (C_4-C_{10})cycloalkyl unsubstituted or substituted with (C_1-C_6)alkyl, or
(iv) phenyl unsubstituted or substituted with 1 to 5 substituents independently selected from: halo, hydroxy, nitro, (C_1-C_{10}) alkyl, (C_1-C_{10})alkoxy, halo-(C_1-C_3)alkoxy, halo-(C_1-C_3)alkyl, (C_1-C_3)alkoxyphenyl, phenyl, phenyl-(C_1-C_3)alkyl, (C_1-C_6)alkoxyphenyl, phenyl-(C_1-C_3)alkynyl, and (C_1-C_6)alkylphenyl;

f) (C_4-C_{10})cycloalkyl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

(i) (C_1-C_6)alkyl,
(ii) (C_1-C_6)alkoxy,
(iii) (C_1-C_6)alkenyl,
(iv) (C_1-C_6)alkynyl,
(v) (C_4-C_{10})cycloalkyl,
(vi) phenyl,
(vii) phenylthio,
(viii) phenyl substituted by nitro, halo, (C_1-C_6)alkanoyloxy, or carbocycloalkoxy, and
(ix) a group represented by the formula -Z-R^{13} wherein Z and R^{13} are as defined above; and

g) a group of the formula:



wherein
A^3 and A^4 are each independently selected from
(i) a bond,
(ii) -O-,
S(iii) $-(O)_t-$, wherein t is 0 to 2,
(iv) $-C(R^{17})_2-$, wherein each R^{17} substituent is independently selected from hydrogen, (C_1-C_6)alkyl, hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, or both R^{17} substituents taken together are O,
(v) $-N(R^{18})_2-$, wherein each R^{18} substituent is independently selected from hydrogen; (C_1-C_6)alkyl; (C_1-C_6)alkenyl; (C_1-C_6)alkynyl; (C_4-C_{10})cycloalkyl; phenyl; phenyl substituted by nitro, halo, (C_1-C_6)alkanoyloxy; or both R^{18} substituents taken together are (C_4-C_{10})cycloalkyl;
R^{16} is R^{12} or R^{13} as defined above; and
u is 0-4.

3. A compound of Claim 1 wherein R is 4-epi-vancosaminyl, R^1 is hydrogen, R^2 is $NHCH_3$, R^3 is $CH_2CH(CH_3)_2$, R^4 is $CH_2(CO)NH_2$, R^5 is hydrogen, R^6 is 4-*epi*-vancosaminyl, and X and Y are Cl.

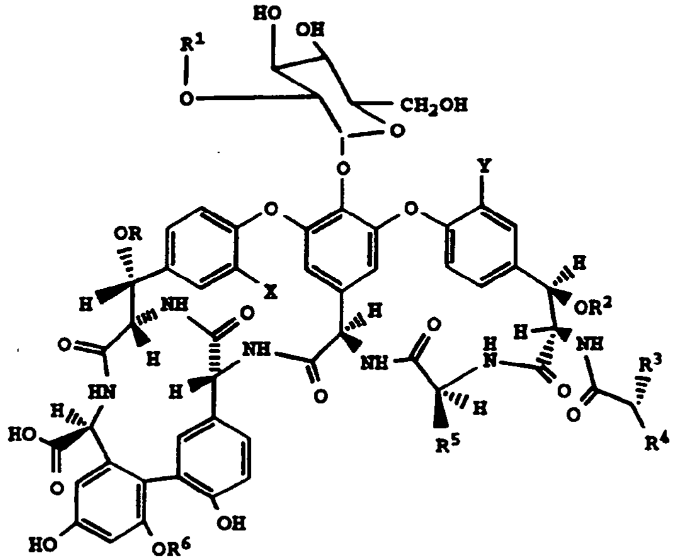
4. A compound of Claim 2 wherein R is 4-*epi*-vancosaminyl, R^1 is hydrogen, R^2 is $NHCH_3$, R^3 is $CH_2CH(CH_3)_2$, R^4 is $CH_2(CO)NH_2$, R^5 is hydrogen, R^6 is 4-*epi*-vancosaminyl, and X and Y are Cl.

5. The compound 4-[4-chlorophenyl]benzyl-A82846B.

6. A pharmaceutical composition comprising a compound of Claim 1 to 5 or a pharmaceutically acceptable salt thereof, associated with one or more pharmaceutically acceptable carriers therefor.

7. A pharmaceutical composition as claimed in Claim 6 for use in treating susceptible bacterial infections.

8. A process for the preparation of a compound of any one of Claims 1 to 5 which comprises
a) reacting in methanol at about 25°C to about 100°C under an inert atmosphere:
i) a glycopeptide antibiotic of the formula:



wherein X and Y are each independently hydrogen or chloro;

R is hydrogen, 4-*epi*-vancosaminyl, actinosaminyl, or ristosaminyl;

R^1 is 4-*epi*-vancosaminyl, acosaminyl, ristosaminyl, 4-keto-vancosaminyl, or vancosaminyl;

R^2 is hydrogen, or mannose;

R^3 is $-NH_2$, $-NHCH_3$, or$-N(CH_3)_2$;

R^4 is $-CH_2CH(CH_3)_2$, [*p*-OH,*m*-Cl]phenyl, *p*-rhamnose-phenyl, [*p*-rhamnose-galactose]phenyl, [*p*-galactose-galactose]phenyl, or [*p*-CH_3O-rhamnose]phenyl;

R^5 is $-CH_2(CO)NH_2$, benzyl, [*p*-OH]phenyl, or [*p*-OH, m-Cl]phenyl;

R^6 is hydrogen, or mannose, with

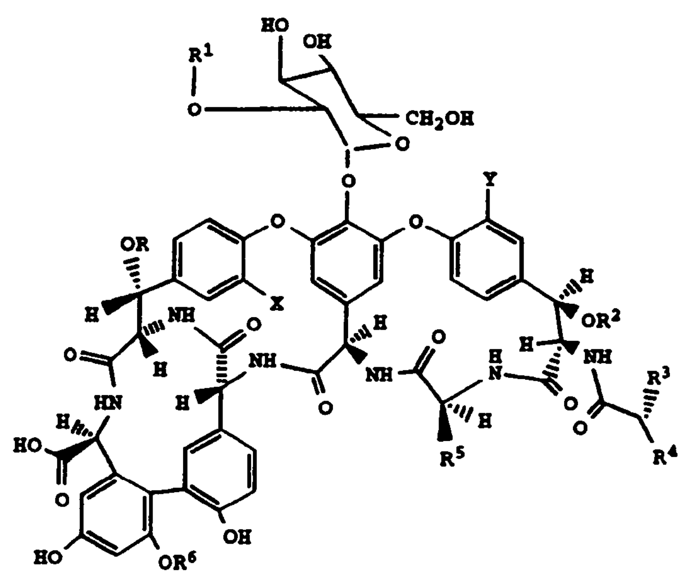
ii) an aldehyde corresponding to the group R^7 as defined in Claim 1 at about 25°C to about 100°C;

b) continuing the reaction until formation of a Schiff's base; and

c) reducing the Schiff's base by addition of a metal borohydride to the mixture at 25°C to about 100°C.

9. A process for the preparation of a compound of any one of Claim 1 to 5 which comprises reacting in a polar solvent at about 25°C to about 100°C under an inert atmosphere:

i) a glycopeptide antibiotic of the formula:



wherein X and Y are each independently hydrogen or chloro;

R is hydrogen, 4-*epi*-vancosaminyl, actinosaminyl, or ristosaminyl;

R^1 is 4-*epi*-vancosaminyl, acosaminyl, ristosaminyl, 4-keto-vancosaminyl, or vancosaminyl;

R^2 is hydrogen, or mannose;

R^3 is $-NH_2$, $-NHCH_3$, or-$N(CH_3)_2$;

R^4 is $-CH_2CH(CH_3)_2$, [*p*-OH,*m*-Cl]phenyl, *p*-rhamnose-phenyl, [*p*-rhamnose-galactose]phenyl, [*p*-galactose-galactose]phenyl, or [*p*-CH_3O-rhamnose]phenyl;

R^5 is $-CH_2(CO)NH_2$, benzyl, [*p*-OH]phenyl, or [*p*-OH, m-Cl]phenyl;

R^6 is hydrogen, or mannose, with

ii) an aldehyde corresponding to the group R^7 as defined in Claim 1, in the presence of

iii) a reducing agent selected from a metal borohydride, and a homogeneous or heterogeneous catalytic hydrogenation agent or agents;

for a time sufficient to produce a compound of Claim 1.

10. The process of Claim 9 wherein the reducing agent is sodium cyanoborohydride, and the reaction is carried out for about 20 to 28 hours at a temperature of about 60°C to about 70°C.

11. The process of Claim 9 wherein the aldehyde is 4'biphenylcarboxaldehyde.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 30 0429

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	JOURNAL OF ANTIBIOTICS., vol.42, no.1, January 1989, TOKYO JP page 63-72 R NAGARAJAN ET AL. 'Synthesis and antibacterial evaluation of N-alkyl vancomycins' * the whole document *	1-10	C07K9/00 A61K38/14
X	EP-A-0 201 251 (ELI LILLY) 12 November 1986 * the whole document *	1-10	
D,A	EP-A-0 435 503 (ELI LILLY) 3 July 1991 * the whole document *	1-10	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)
C07K
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	9 May 1995	Masturzo, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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